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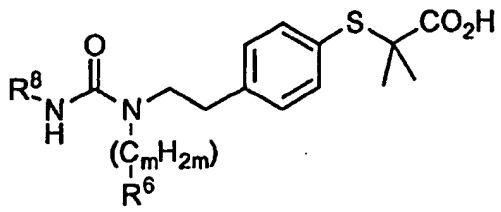

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(57) Abstract

Novel compounds of Formula (1) and esters, salts, and physiologically functional derivatives thereof are disclosed. Methods for preparing and using the compounds are also disclosed. Many of these compounds are selective activators of PPAR alpha. The compounds are particularly useful for treating obesity.

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CHEMICAL COMPOUNDS

Field of the Invention

The present invention relates to certain novel PPAR alpha activating compounds, processes for their preparation, pharmaceutical compositions containing the compounds, and uses of the compounds as therapeutic agents.

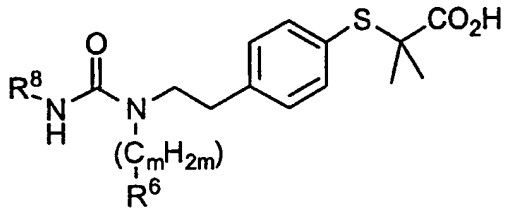
Obesity can be described as a state of excessive accumulation of body fat, and is widely considered to be a major public health problem. Treatment of obesity remains a problem.

Certain fibrate compounds are described in WO92/10468. Such compounds are said to be useful in the prophylaxis and treatment of atherosclerosis.

PCT publication WO95/18533 describes methods of identifying activators and antagonists of peroxisome proliferator activated receptor ("PPAR") and activators of retinoic acid receptor gamma. The disclosure discusses treating obesity.

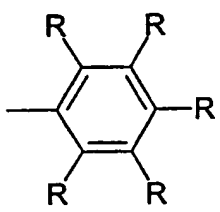
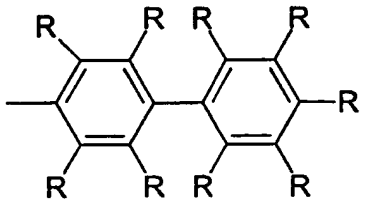
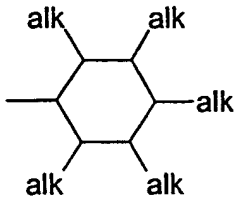
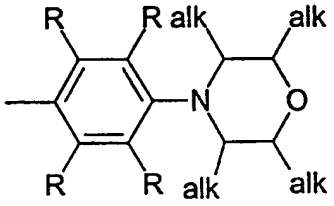
Brief Description of the Invention

Briefly, in one aspect, the present invention provides compounds of Formula (1) and esters, salts, and physiologically functional derivatives thereof

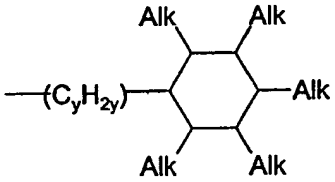
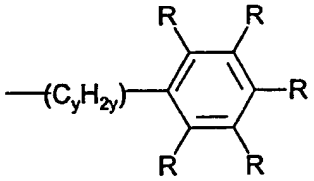


(1)

wherein m is from 0 to 20, R^6 is selected from the group consisting of hydrogen and

and R^8 is selected from the group consisting of

where y is 0, 1, or 2, each alk is independently hydrogen or alkyl group containing 1 to 6 carbon atoms, each R group is independently hydrogen, halogen, cyano, $-NO_2$, phenyl, straight or branched alkyl or fluoroalkyl containing 1 to 6 carbon atoms and which can contain hetero atoms such as nitrogen, oxygen, or sulfur and which can contain functional groups such as ketone or ester, cycloalkyl containing 3 to 7 carbon atoms, or two R groups bonded to adjacent carbon atoms can, together with the carbon atoms to which they are bonded, form an aliphatic or aromatic ring or multi ring system, and where each depicted ring has no more than 3 alk groups or R groups that are not hydrogen. Preferably, the compounds of Formula (1) are PPAR alpha activating compounds.

The compounds of Formula (1) are generally PPAR alpha activating compounds, and therefore are useful in the treatment of a PPAR alpha

mediated disease, risk factor, or condition, in particular, obesity and dyslipidemia. Therefore, in another aspect of the invention there is provided a method of treating a PPAR alpha mediated disease, risk factor, or condition, in particular obesity and dyslipidemia, comprising administering to an individual in need thereof a therapeutically effective amount of a PPAR alpha activating compound of Formula (1). The invention further provides the use of a PPAR alpha activating compound of Formula (1) for the manufacture of a medicament for the treatment of a PPAR alpha mediated disease, risk factor, or condition, in particular obesity and dyslipidemia.

The invention further provides compounds of Formula (1) for use in therapy, and pharmaceutical compositions comprising a compound of Formula (1).

The invention also provides methods for preparing the compounds and pharmaceutical compositions of the invention.

As used herein, unless otherwise indicated, the term alkyl or words containing the terms such as fluoroalkyl, can be either straight chain or branched chain. For example, a 3-carbon alkyl group can be either n-propyl or i-propyl.

Detailed Description of the Invention

Preferably, the compounds of Formula (1) are PPAR alpha activating compounds. More preferable compounds are those that, in addition to being PPAR alpha activating compounds, are selective activators of PPAR alpha. By "PPAR activating compound", or "PPAR activator", or the like, is meant those compounds which achieve 50% activation of human PPAR ("hPPAR") alpha (in the Transfection assay described below) at concentrations of 10^{-5} M or less, as exemplified in the working examples. By selective, is meant those compounds which selectively activate PPAR alpha over PPAR gamma such that the ratio

$$\frac{EC_{50}\ \text{PPAR Gamma}}{EC_{50}\ \text{PPAR Alpha}}$$

is at least 10, as exemplified in the working examples. Most preferred are those compounds such that this ratio is at least 100.

Preferably, each R^6 and R^8 has no more than 2 R groups and no more than 2 alk groups that are other than hydrogen. Most preferably, all R groups and all alk groups are hydrogen.

Particularly preferred compounds are those where y is 0, m is from 0 to 6, and each alk and each R group is hydrogen.

Examples of suitable compounds of Formula (1) are

2-(4-(2-(1-(4-Biphenylethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

2-(4-(2-(1-(2-(4-Morpholinophenyl)ethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

2-(4-(2-(1-(Cyclohexanebutyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

2-(4-(2-(1-Heptyl-3-(2,4-difluorophenyl)ureido)ethyl)phenylthio)-2-methylpropionic acid

2-(4-(2-(1-(2-Chloro-4-(2-trifluoromethylphenyl) phenylmethyl)-3-(cyclohexyl)ureido)ethyl)phenylthio)-2-methylpropionic acid

and esters, salts, and physiologically functional derivatives thereof.

Particularly preferred compounds of Formula (1) are

2-(4-(2-(1-(4-Biphenylethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

2-(4-(2-(1-(2-(4-Morpholinophenyl)ethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

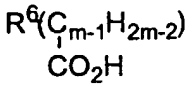
2-(4-(2-(1-(Cyclohexanebutyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

and esters, salts, and physiologically functional derivatives thereof.

The compounds of this invention can be prepared in a variety of ways. For example, the compounds of Formula (1) can be prepared by reacting the compounds of Formulas (2), (3), and (4),

R^8-NCO

(2)



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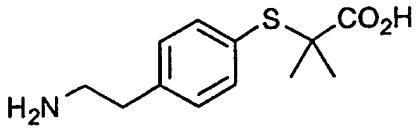


(4)

to give compounds of the invention of Formula (1) wherein R^6, R^8, and m are as defined above. Synthetic routes will also be illustrated in the working examples below.

The compounds of the present invention may be utilized in the form of a pharmaceutically acceptable salt or solvate thereof. Preferred salts of compounds of Formula (1) are those that are physiologically acceptable. However, non-physiologically acceptable salts are within the scope of the present invention for use as intermediates in the preparation of the compounds of the invention and their physiologically acceptable salts and physiologically functional derivatives.

The "physiologically functional derivatives" referred to herein are compounds which are converted in vivo to a compound of Formula (1) or one of its physiologically acceptable salts.

Many of the compounds of this invention will contain one or more stereocenters. The present invention includes all possible stereoisomers, tautomers, and geometric isomers of the compounds, including optically enriched compositions as well as the racemic mixtures. When an enantiomerically enriched composition is desired, it may be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method. See, for example, Stereochemistry of Carbon Compounds, by E. L. Eliel (Mcgraw Hill, 1962) and Tables of Resolving Agents, by S.H. Wilen.

Reference to "treatment" includes prophylaxis as well as the treatment of established of established diseases or symptoms. Moreover, it will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of that attendant physician or veterinarian.

PPAR alpha, gamma, and delta are recognized subtypes of PPARs. The PPARs are known to bind to their target genes as heterodimers with RXR. The

present invention provides PPAR alpha activating compounds for use in the treatment of obesity, dyslipidemia, and other PPAR alpha mediated diseases, conditions, or risk factors. More particularly, the present invention provides PPAR alpha activators useful in the treatment of Alzheimer's disease, atherosclerosis, obesity, inflammation, cancer, psoriasis, pancreatitis, and various disease risk factors. Most preferably the PPAR alpha activators are selective. Disease risk factors may include dyslipidemia, hypertriglyceridemia, hyperlidipemia, and hypercholesterolemia. See, for example, K.M. Anderson, et al., *An Updated Coronary Risk Profile*, AHA Medical/Scientific Statement Science Advisory, vol. 83, pp 356-362 (1991), W.P. Castilli, *The Triglyceride Issue: A View From Farmingham*, Am. Heart J., vol. 112, pp 432-437 (1986), M. Austin, *Plasma Triglyceride and Coronary Heart Disease*, Arteriosclerosis and Thrombosis, vol. 11, pp 2-14 (1991), and J.J. Genest, et al., *Prevalence of Familial Lipoprotein Disorders in Patients With Premature Coronary Artery Disease*, vol. 85, pp 2025-2033 (1992). PPAR Alpha agonists have been shown to have antitumor activity. See, for example, Samid et al, Biochem. Pharmacol. (1996) 52, 659-667. PPAR Alpha agonists have been shown to have antiinflammatory activity. See, for example, Wahli et. al., Nature (1996) 384, 39-43. PPAR Alpha agonists have been shown to have antiatherosclerotic activity. See, for example, Staels et. al., Nature (1998) p790.

A recognized clinical and epidemiological measure for the classification of obesity is the Body Mass Index (BMI) which is defined as weight in kilograms divided by the square of height in meters. Typically, a BMI of 25-30 is considered as overweight and >30 as obese. Treatment according to the present invention generally refers to a lowering of BMI to less than about 29 to 31. It will however be appreciated by persons skilled in the art that obesity is inherently difficult to classify, and that the cut-off point for the definition of obesity is necessarily arbitrary, in part because body fatness is a continuum. However, in general terms treatment according to the present invention desirably prevents or alleviates obesity to an extent whereby there is no longer a significant health risk to the patient.

The amount of a PPAR alpha activator which is required to achieve the desired biological effect will, of course, depend on a number of factors, for

example, the mode of administration and the precise clinical condition of the recipient. In general, the daily dose will be in the range of 0.01mg - 1g/kg, typically 0.1 - 100mg/kg. An intravenous dose may, for example, be in the range of 0.001mg to 0.1g/kg, typically 0.01mg to 10mg/kg, which may conveniently be administered as an infusion of from 0.1μg to 1mg, per minute. Infusion fluids suitable for this purpose may contain, for example, from 0.01μg to 0.1mg, per milliliter. Unit doses may contain, for example, from 0.01μg to 1g of a PPAR alpha activator. Thus ampoules for injection may contain, for example, from 0.01μg to 0.1g and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 0.1mg to 1g.

A compound of this invention may be employed in the treatment of a disease or condition as the compound per se, but is preferably presented with an acceptable carrier in the form of a pharmaceutical formulation. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the activator as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the activator.

The formulations include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges or tablets, each containing a predetermined amount of a PPAR alpha activator; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. In general, the formulations are prepared by uniformly and intimately admixing the active PPAR alpha activator with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or molding a powder or granules of the PPAR alpha activator optionally with one or more accessory ingredients. Compressed

tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a PPAR alpha activator in a flavored base, usually sucrose and acacia or tragacanth, and pastilles comprising the activator in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of a PPAR alpha activator, preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the activator with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the activator.

Formulations suitable for rectal administration are preferably presented as unit-dose suppositories. These may be prepared by admixing a PPAR alpha activator with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include Vaseline, lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The PPAR alpha activator is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

Experimental

The following examples are given in illustration of, but not limitation of, the invention. Each of the following Examples of the invention showed 50%

activation of hPPAR alpha at concentration of 10^{-5}M or less and are therefore, activators of hPPAR alpha. It is possible to prepare a large variety of the compounds of Formula (1) using standard solid phase synthetic methods such as those illustrated in the following working examples. The prepared compounds can then readily be screened for activity and selectivity using the Transfection assay described below. By using these techniques, one can readily determine which compounds of Formula (1) are activators of PPAR alpha and which compounds of Formula (1) are selective activators of PPAR alpha. In addition, the highly efficient Binding assay described below can be used to quickly pre-screen large numbers of compounds and those compounds that are shown to bind can then be screened for activity and selectivity.

Intermediate 1

t-Butyl 2-(4-bromophenylthio)-2-methylpropionate

A mixture of 4-bromothiophenol (100 g; 0.53 mole) and potassium hydroxide (29.5 g; 0.53 mole) in ethanol (1000 mL) was stirred until all material had dissolved. t-Butyl 2-bromoisobutyrate (117.6 g; 0.53 mole) was added dropwise over 30 min, keeping the temperature below 55°C. The resulting mixture was heated at reflux for 1 h, then cooled to 23°C. The precipitate (KBr) was removed by filtration and the solvent evaporated. The residue was partitioned between water (1000 mL) and methylene chloride (500 mL) and the organic layer was separated, dried (Na_2SO_4) and evaporated to afford a white solid. Crystallization from hexane gave a white solid (119.85 g; 68%).

^{1}H-NMR ($CDCl_3$) δ 7.41 (d, 2H, J=7.5 Hz), 7.35 (d, 2H, J=7.5 Hz), 1.40 (s, 15H).

Intermediate 2

t-Butyl 2-(4-(2-phthalimidoethenyl)phenylthio)-2-methylpropionate

A mixture of Intermediate 1 (50 g; 150 mmole), N-vinylphthalimide (27.2 g; 157 mmole), palladium acetate (1.68 g; 7.5 mmole), tri-o-tolylphosphine (3.07 g; 15 mmole) and triethylamine (42 mL) in a sealed tube was gently heated until all solids had dissolved then heated at 110°C for 15 h. The solvent was evaporated and the

residue partitioned between 2N HCl (300 mL) and ethyl acetate (300 mL) and filtered through celite. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and evaporated. The residue was purified by chromatography using EtOAc-Hexane-CH_2Cl_2 as eluent to afford a yellow solid (43.14 g; 68%).

^{1}H-NMR ($CDCl_3$) δ 7.90 (dd, 2H, J=3.3 Hz, J'=5.4 Hz), 7.76 (dd, 2H, J=3.3 Hz, J'=5.4 Hz), 7.64 (d, 1H, J=15.3 Hz), 7.48 (d, 2H, J=8.4 Hz), 7.41 (d, 2H, J=8.4 Hz), 7.37 (d, 1H, J=15.3 Hz), 1.45 (s, 6H), 1.43 (s, 9H).

Intermediate 3

t-Butyl 2-(4-(2-phthalimidoethyl)phenylthio)-2-methylpropionate

A solution of Intermediate 2 (43.1 g; 100 mmole) in THF (600 mL) was added to a suspension of Wilkinson's Catalyst (tris(triphenylphosphine)rhodium chloride) (5 g) in ethanol (100 mL) and the mixture stirred under an atmosphere of hydrogen (20 psi) for 5 h. The solvent was evaporated and the residue was purified by chromatography using EtOAc-Hexane-CH_2Cl_2 as eluent to afford a light brown solid (37g).

^{1}H-NMR ($CDCl_3$) δ 7.82 (dd, 2H, J=3.4 Hz, J'=5.6 Hz), 7.70 (dd, 2H, J=3.4 Hz, J'=5.6 Hz), 7.41 (d, 2H, J=8.0 Hz), 7.20 (d, 2H, J=8.0 Hz), 3.91 (t, 2H, J=7.8 Hz), 2.98 (t, 2H, J=7.8 Hz), 1.40 (s, 9H), 1.39 (s, 6H).

Intermediate 4

t-Butyl 2-(4-(2-aminoethyl)phenylthio)-2-methylpropionate

A solution of Intermediate 3 (29.3 g; 69 mmole) in ethanol (500 mL) was treated with hydrazine hydrate (20 g; 350 mmole) and the resulting mixture heated at reflux for 1 h and left to stand at 23°C for 15 h. The resultant solid was removed by filtration, the solvent evaporated, and the residue partitioned between 1N NaOH (150 mL) and ether (1300 mL). The organic layer was separated and washed with 1N NaOH (100 mL) and brine, dried ($MgSO_4$) and evaporated to afford an oil (19.9 g; 97%). ^{1}H-NMR ($CDCl_3$) δ 7.42 (d, 2H, J=8.0 Hz), 7.14 (d, 2H, J=8.0 Hz), 2.98 (br, 2H), 2.78 (t, 2H, J=7.0 Hz), 2.51 (br , 2H), 1.41 (s, 15H).

Intermediate 5

t-Butyl 2-(4-(2-(fluoren-9-ylmethyloxycarbonylaminoethyl)phenylthio)-2-methylpropionate

A solution of Intermediate 4 (37.9 g; 130 mmole) in dioxane (100 mL) was treated with a solution of sodium carbonate (13.6 g; 130 mmole) in water (200 mL) followed by a slurry of Fmoc-OSu (43.3 g; 130 mmole) in dioxane (100 mL) and the mixture was stirred at 23°C for 5 h. The organic solvent was evaporated and the residue was acidified with 1N HCl. The organic material was extracted with CH_2Cl_2 (2 x 200 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography using 15 then 20% EtOAc-Hexane as eluent to afford a gum (49.3 g; 74%). ^{1}H-NMR ($CDCl_3$) δ 7.77 (d, 2H, J=7.6 Hz), 7.57 (d, 2H, J=7.6 Hz), 7.44 (d, 2H, J=8.0 Hz), 7.31 (t, 2H, J=7.2 Hz), 7.13 (d, 2H, J=8.0 Hz), 4.77 (m, 1H), 4.42 (d, 2H, J=6.8 Hz), 4.21 (t, 1H, J=6.8 Hz), 3.44 (q, 2H, J=6.4 Hz), 2.81 (t, 2H, J=6.8 Hz), 1.44 (s, 6H), 1.42 (s, 9H).

Intermediate 6

2-(4-(2-(Fluoren-9-ylmethyloxycarbonylamino)ethyl)phenylthio)-2-methylpropionic acid

A solution of Intermediate 5 (27.1 g; 52 mmole) in TFA (135 mL) and CH_2Cl_2 (135 mL) was stirred at 23°C for 5 h. The solvent was evaporated and the residue dissolved in CH_2Cl_2 (200 mL) and washed with water (3 X 150 mL) and brine (2 X 100 mL), dried ($MgSO_4$) and evaporated to afford a low melting solid (22.9 g; 95%). ^{1}H-NMR ($CDCl_3$; complicated by rotamers) δ 9.25 (br, 1H), 7.76 (d, 2H, J=7.2 Hz), 7.56 (d, 2H, J=7.2 Hz), 7.46 (d, 2H, J=7.6 Hz), 7.39 (t, 2H, J=7.2 Hz), 7.30 (t, 2H, J=7.2 Hz), 7.13 (d, 2H, J=7.6 Hz), 4.88 (br, 0.6H), 4.54 (br, 0.4H), 4.40 (d, 1.2H, J=6.8 Hz), 4.19 (t, 0.8H, J=6.8 Hz), 3.43 (q, 1.2H, J=6.4 Hz), 3.17 (br, 0.8H), 2.80 (t, 1.2H, J=7.2 Hz), 2.53 (br, 0.8 Hz), 1.50 (s, 6H). Analysis Found: C, 68.97; H, 6.04; N, 2.95. $C_{27}H_{27}NO_4So0.5H_2O$ Requires: C, 68.91; H, 6.00; N, 2.98%.

Intermediate 7

Intermediate 6 loaded onto SASRIN® resin

A solution of Intermediate 6 (9.66g, 20.93 mmole), 4-dimethylaminopyridine (256 mg; 2.093 mmole) and diisopropylcarbodiimide (2.635 g; 20.88 mmole) in CH_2Cl_2 (40 mL) was stirred at 23°C for 10 min. SASRIN® resin (4.7 g; 0.89 mmol/g; 4.186 mmole) was added and the resulting solution stirred at 23°C for 1.5 h. The resin was filtered and washed with CH_2Cl_2 (3 X 100 mL) then suspended in CH_2Cl_2 (40 mL) and treated with diisopropylethylamine (7 mL) and isovaleric anhydride (4 mL). After stirring at 23°C for 1 h, the resin was filtered and washed with CH_2Cl_2 (3 x 75 mL), DMF (3 x 75 mL), MeOH (3 x 75 mL) then CH_2Cl_2 (3 x 75 mL) and dried in vacuum. Resin loading was determined by standard FMOC analysis (0.3-0.43 mmole/g).

Intermediate 8

t-Butyl N-(Cyclohexylbutanoyl)-2-(4-(2-aminoethyl)phenylthio)-2-methylpropionate

A solution of Intermediate 4 (77 g; 260.6 mmole) and cyclohexanebutanoic acid (66.55 g; 390.9 mmole) in CH_2Cl_2 (500 mL) was treated with $HOBToH_2O$ (20 g; 130.7 mmole) and diisopropylcarbodiimide (112.6 g; 521.2 mmole) and the resulting solution stirred at 23°C for 15 h. The solution was washed with saturated $NaHCO_3$ solution, 1N HCl and brine and the organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by chromatography using 20% EtOAc-Hexane as eluent to afford a white solid (100.7 g; 86%). ^{1}H-NMR ($CDCl_3$) δ 7.42 (d, 2H, J=8.0 Hz), 7.13 (d, 2H, J=8.0 Hz), 5.87 (br s, 1H), 3.49 (q, 2H, J=6.8 Hz), 2.81 (t, 2H, J=7.2 Hz), 2.12 (t, 2H, J=7.6 Hz), 1.73-1.52 (m, 7H), 1.41 (s, 15H), 1.26-1.07 (m, 6H), 0.84 (m, 2H).

Intermediate 9

t-Butyl 2-(4-(2-(Cyclohexylbutylamino)ethyl)phenylthio)-2-methylpropionate

A solution of Intermediate 8 (5 g; 5.92 mmole) in THF (50 mL) was treated with a 1M solution of borane in THF (40 mL; 40 mmole) and the mixture allowed to stand at 23°C for 15 h. Excess borane was destroyed by the careful addition of n-butanol (20 mL) and the resulting solution heated under reflux for 2h. The solvent was evaporated the residue was purified by chromatography using EtOAc then 10%

MeOH-EtOAc as eluent to afford an oil (3.78 g; 66%). ^{1}H-NMR ($CDCl_3$) δ 7.41 (d, 2H, J=8.0 Hz), 7.14 (d, 2H, J=8.0 Hz), 2.84 (m, 4H), 2.61 (t, 2H, J=7.2 Hz), 2.05 (br, 1H), 1.65 (m, 6H), 1.41 (s, 15H), 1.33-1.07 (m, 6H), 0.82 (m, 2H).

Intermediate 10

t-Butyl 2-(4-(2-(1-(Cyclohexanebutyl)-3-cyclohexylureido)ethyl) phenylthio)-2-methylpropionate

A solution of Intermediate 9 (5 g; 11.5 mmole) and cyclohexylisocyanate (1.73 g; 13.8 mmole) in CH_2Cl_2 (50 mL) was allowed to stand at 23°C for 18h. The solvent was evaporated and the residue purified by chromatography using 10% EtOAc-Hexane as eluent to afford a white solid (5.3 g; 83%). ^{1}H-NMR ($CDCl_3$) δ 7.42 (d, 2H, J=8.1 Hz), 7.15 (d, 2H, J=8.1 Hz), 4.01 (d, 1H, J=7.8 Hz), 3.61 (m, 1H), 3.39 (t, 2H, J=7.5 Hz), 3.03 (t, 2H, J=7.5 Hz), 2.83 (t, 2H, J=7.5 Hz), 1.90 (m, 2H), 1.74-1.52 (m, 8H), 1.42 (s, 15H), 1.50-0.96 (m, 15H), 0.85 (m, 2H).

Example 1

2-(4-(2-(1-(Cyclohexanebutyl)-3-cyclohexylureido)ethyl) phenylthio)-2-methylpropionic acid

A solution of Intermediate 9 (5g; 8.96 mmole) in CH_2Cl_2 (40 mL) and TFA (40 mL) was allowed to stand at 23°C for 4 h. The solvent was evaporated to afford a semi-solid, which was purified by chromatography using 5-20% MeOH-CH_2Cl_2 as eluent to afford a white solid (3.7 g; 82%). ^{1}H-NMR ($CDCl_3$) δ 9.05 (br, 1H), 7.44 (d, 2H, J=8.0 Hz), 7.15 (d, 2H, J=8.0 Hz), 4.28 (br, 1H), 3.63 (br s, 1H), 3.41 (t, 2H, J=7.4 Hz), 3.01 (t, 2H, J=7.6 Hz), 2.83 (t, 2H, J=7.2 Hz), 1.89 (m, 2H), 1.72-1.52 (m, 8H), 1.42 (s, 6H), 1.52-0.95 (m, 15H), 0.85 (m, 2H).

The following Example was prepared using the procedures outlined for the preparation of Example 1.

Example 2 2-(4-(2-(1-(4-Biphenylethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

General Method

General solid phase synthesis method for preparation of 2-(4-(2-(Substituted ureido)ethyl)phenylthio)-2-methylpropionic acids

40 mg of Intermediate 7 (0.43 mmol/g) was suspended in 1 mL of 20% piperidine in DMF for 30 min. The solution was drained and the resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2, THF, and DMF. A solution of a carboxylic acid (1M in DMF, 0.17 mL), HOBT (1M in DMF, 0.17 mL), and DIC (1M in DMF, 0.17 mL) were added. The suspension was mixed and then stood at room temperature for 2 h. The solution was drained and the resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2, and THF. A solution of BH_3oTHF (1M in THF, 0.52 mL) was added. The suspension was mixed and then stood at room temperature for 18 h. The solution was drained and the resin was washed with THF, CH_2Cl_2, DMF, MeOH, CH_2Cl_2 and DMF. A solution of an isocyanate (1M in DMF, 0.52 mL) was added. The suspension was mixed and then stood at room temperature for 18 h. The solution was drained and the resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2, THF, and CH_2Cl_2. The resulting resin was suspended in 1 mL of 10% TFA in CH_2Cl_2 for 30 min. The solution was filtered and the filtrate evaporated to yield the 2-(4-(2-(Substituted ureido)ethyl)phenylthio)-2-methylpropionic acid.

Using the **General Method**, the following example was synthesized from Intermediate 7.

Example 3 2-(4-(2-(1-(2-Chloro-4-(2-trifluoromethylphenyl) phenylmethyl)-3-(cyclohexyl)ureido)ethyl)phenylthio)-2-methylpropionic acid

Intermediate 11

2-(4-(2-(Phenylmethyloxycarbonylamino)ethyl)phenoxy)-2-methylbutanoic acid

A solution of 4-(2-(phenylmethyloxycarbonylamino)ethyl)phenol (5.74 g; 21.16 mmole) in 2-butanone (17 mL) and chloroform (6 g) was added dropwise to a mixture of sodium hydroxide (9.0 g; 225 mmole) and 2-butanone (67 mL) whilst keeping the reaction temperature below 30°C. The mixture was allowed to stir at 30°C for 4h. Ether (100 mL) was added and the resultant solid was collected by

filtration and washed with ether (100 mL). The solid was dissolved in water (70 mL) and any residual ether removed by evaporation. 1N Hydrochloric acid was added to adjust the pH to 1, and the resulting oil was extracted with dichloromethane (3 x 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated to afford a yellow oil (3.82 g; 49%).

^{1}H-NMR ($CDCl_3$) δ 7.26 (s, 5H), 7.09 (d, 2H, J=7.9 Hz), 6.88 (d, 2H, J=8.4 Hz), 5.09 (s, 2H), 4.75 (br s, 1H), 3.42-3.44 (m, 2H), 2.75 (t, 2H, J=6.7 Hz), 1.92-2.00 (m, 2H), 1.47 (s, 3H), 1.04 (t, 3H, J=2.6 Hz). Mass spectrometry ES^-, m/e $(M+H)^+$=372.

Intermediate 12

Methyl 2-(4-(2-(phenylmethyloxycarbonylamino)ethyl)phenoxy)-2-methyl butyrate

A solution of Intermediate 11 (2.0 g; 5.38 mmole) in dimethylformamide (12 mL) was treated with potassium carbonate (2.23 g; 16.14 mmole) and methyl iodide (1.54 g; 10.76 mmole) and the resulting mixture stirred at 23°C for 2h. The mixture was filtered and the solid collected was washed with ethyl acetate (70 mL). The filtrate was washed with brine (4 x 50 mL), dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel using hexane then 33% ethyl acetate-hexane as eluent to afford a colorless oil (1.27 g; 61%).

^{1}H-NMR (DMSO-d_6) δ 7.31 (m, 5H), 7.06 (d, 2H, J=8.4 Hz), 6.68 (d, 2H, J=8.4 Hz), 4.98 (s, 2H), 3.67 (s, 3H), 3.15 (m, 2H), 2.62 (t, 2H, J=7.1 Hz), 1.86 (m, 2H), 1.38 (s, 3H), 0.86 (t, 3H, J=7.3 Hz). Mass spectrometry ES^+, m/e $(M+Na)^+$ = 408.

Intermediate 13

Methyl 2-(4-(2-aminoethyl)phenoxy)-2-methyl butyrate acetate salt

A solution of Intermediate 12 (1.27 g; 3.29 mmole) in methanol (50 mL) and acetic acid (0.4 g) was treated with 10% palladium on carbon and shaken in a hydrogen atmosphere (50 psi) for 2h. The catalyst was filtered through celite and the solvent was evaporated to afford a yellow oil in quantitative yield (1.04 g).

^{1}H-NMR ($CDCl_3$): δ 7.06 (d, 2H, J=8.4 Hz), 6.77 (d, 2H, J=8.4 Hz), 6.70 (br s, 2H), 3.76 (s, 3H), 3.02 (br s, 2H), 2.82 (m, 2H), 1.99 (s, 3H), 1.92 (m, 2H), 1.48 (s, 3H), 0.96 (t, 3H, J=7.4 Hz). Mass spectrometry ES^+, m/e $(M+H)^+$=252.

Intermediate 14

Methyl 2-(4-(2-(2,4-dinitrophenylsulfonylamino)ethyl)phenoxy)-2-methyl butyrate

A solution of Intermediate 13 (2 g; 6.42 mmole) in CH_2Cl_2 (40 mL) was treated with saturated sodium bicarbonate solution and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (5 x 50 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated to afford the free base as a yellow oil (1.61 g; 100%). This was dissolved in CH_2Cl_2 (40 mL) and treated with pyridine (0.45 g; 5.61 mmole) and 2,4-dinitrophenylsulfonyl chloride (1.5 g; 5.61 mmole), and the mixture was allowed to stir at 23°C for 3h. Water (60 mL) was added and the organic layer separated, washed with water (3 X 40 mL) and saturated sodium bicarbonate (40 mL). The organic layer was dried (Na_2SO_4) and evaporated and the residue purified by chromatography using 15-20% EtOAc-Hexane as eluent to afford a light yellow solid (1.38 g; 51%).

^{1}H-NMR ($CDCl_3$): δ 8.63 (d, 1H, J=2.3 Hz), 8.49 (dd, 1H, J=8.4 Hz, J'=2.3 Hz), 8.07 (d, 1H, J=8.4 Hz), 6.89 (d, 2H, J=8.4 Hz), 6.54 (d, 2H, J=8.4 Hz), 5.34 (t, 1H, J=5.3 Hz), 3.78 (s, 3H), 3.48 (q, 2H, J=8.3 Hz), 2.75 (t, 2H, J=6.6 Hz), 1.92 (m, 2H), 1.42 (s, 3H), 0.93 (t, 3H, J=7.5 Hz).

Intermediate 15

Methyl 2-(4-(2-((2,4-dinitrophenylsulfonyl)(hept-2-en-1-yl))amino)ethyl)phenoxy)-2-methyl butyrate

A solution of Intermediate 14 (315 mg; 0.654 mmole) in THF (15 mL) was treated with triphenylphosphine (343 mg; 1.308 mmole), hept-2-en-1-ol (150 mg; 1.308 mmole) and diethylazodicarboxylate (228 mg; 1.308 mmole) and the mixture allowed to stir at 23°C for 1h. The solvent was evaporated and the residue purified by chromatography using 10-15% EtOAc-Hexane as eluent to afford a semi-solid (400 mg; >100%). TLC and NMR shows that the desired compound is present along with 1,2-(diethoxycarbonyl)hydrazine.

Intermediate 16

Methyl 2-(4-(2-(hept-2-en-1-ylamino)ethyl)phenoxy)-2-methyl butanoate

A solution of Intermediate 15 (400 mg; 0.654 mmole) in CH_2Cl_2 (5 mL) was treated with triethylamine (132 mg; 1.308 mmole) and mercaptoacetic acid (78 mg; 0.85 mmole) and the mixture was allowed to stir at 23°C for 1h. The mixture was diluted with EtOAc (30 mL) and washed with water (3 X 20 mL) and aqueous sodium bicarbonate (30 mL). The organic layer was dried (Na_2SO_4), evaporated and the residue purified by chromatography using 10% EtOAc-Hexane then 50% EtOAc-Hexane then MeOH as eluent to afford an oil (177 mg; 78% from intermediate 24). ^{1}H-NMR ($CDCl_3$): δ 7.06 (d, 2H, J=7.5 Hz), 6.75 (d, 2H, J=7.5 Hz), 5.59 (m, 2H), 3.76 (s, 3H), 3.30 (d, 2H, J=6.3 Hz), 2.87 (m, 4H), 1.96 (m, 4H), 1.47 (s, 3H), 1.28 (m, 5H), 0.96 (t, 3H, J=7.6 Hz), 0.86 (t, 3H, J=6.9 Hz).

Intermediate 17

Methyl 2-(4-(2-(1-hept-2-enyl-3-(2,4-difluorophenyl)ureido)ethyl)phenoxy)-2-methylbutyrate

A solution of Intermediate 16 (157 mg; 0.452 mmole) in methylene chloride (5 mL) was treated with 2,4-difluorophenylisocyanate (140 mg; 0.904 mmole) and the mixture allowed to stand at 23°C for 18h. The solvent was evaporated and the residue purified by chromatography on silica gel using 10% then 15% ethyl acetate-hexane as eluent to afford a yellow semi-solid (212 mg; 93%). Contaminated with bis-(2,4-difluorophenyl)urea which co-elutes on column.
^{1}H-NMR ($CDCl_3$): δ 8.85 (br s, 1H), 8.02 (m, 1H), 7.09 (d, 2H, J=8.4 Hz), 6.77-6.90 (m, 4H), 5.70 (m, 1H), 5.36 (m, 1H), 3.76 (s, 3H), 3.54 (t, 2H, J=7.3 Hz), 2.84 (t, 2H, J=7.1 Hz), 1.55 (br s, 1H), 1.46 (s, 3H), 1.25-1.35 (m, 5H), 0.96 (t, 3H, J=7.3 Hz), 0.88 (t, 3H, J=7.4 Hz). Mass spectrometry CI/AP$^+$, m/e $(M+H)^+$=503.

Radioligand Precursor

2-(4-(2-(1-Hept-2-enyl-3-(2,4-difluorophenyl)ureido)ethyl) phenoxy)-2-methylbutanoic acid

A solution of Intermediate 17 (370 mg; 0.736 mmole) in methanol (15 mL) was treated with 1N NaOH (7.5 mL) and the mixture heated under reflux for 2h. The mixture was acidified with 1N HCl and extracted with ethyl acetate (3 x 25 mL). The

combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel using 20% ethyl acetate-hexane then ethyl acetate as eluent to afford a tan oil (280 mg; 78%). ^{1}H-NMR ($CDCl_3$) δ 7.95-8.09 (m,1H), 7.14 (d, 2H, J=7.1 Hz), 6.90 (d, 2H, J=7.4 Hz), 6.81 (d, 2H, J=5.2 Hz), 5.66 (m, 1H), 5.37 (m,1H), 3.56 (t, 2H, J=7.4 Hz), 2.87 (t, 2H, J=7.4 Hz), 2.00 (m, 4H), 1.44 (s, 3H), 1.27 (m, 6H), 1.03 (t, 3H, J=7.3 Hz), 0.88 (t, 3H, J=7.3 Hz). Mass spectrometry ES^-, m/e $(M+H)^+$ = 489.

Radioligand

2-(4-(2-(2,3-Ditritio-1-heptyl-3-(2,4-difluorophenyl)ureido)ethyl) phenoxy)-2-methylbutanoic acid

A solution of the Radioligand precursor (10 mg) in anhydrous DMF (3.5 mL) was transferred to a reaction vessel containing 10 % Pd/C (9.8 mg). The reaction vessel was evacuated and degassed via one freeze-thaw-evacuation cycle and then exposed to tritium gas (10.1 Ci). After 4h, the mixture was filtered through celite, evaporated and the residue dissolved in acetonitrile. A portion of this solution (0.8 mL, 26.6 mCi) was purified by HPLC (Dynamax C8, 25 min gradient from 4:1 acetonitrile:0.1%TFA to 9:1 acetonitrile: 0.1% TFA, 235 nm). Fractions containing pure material were combined and evaporated under nitrogen. The residue was redissolved in acetonitrile to provide a solution of the title compound (82.0 Ci/mmol, radiochemical purity, 99%).

The above Radioligand was used in the binding assay described below to show that compounds which were active in the transfection assay were also ligands for PPAR Alpha.

Cold Radioligand

2-(4-(2-(1-Heptyl-3-(2,4-difluorophenyl)ureido)ethyl) phenoxy)-2-methylbutanoic acid

A solution of the Radioligand precursor (10 mg) in anhydrous DMF (3.5 mL) was transferred to a reaction vessel containing 10 % Pd/C (9.8 mg). The reaction vessel was evacuated and degassed via one freeze-thaw-evacuation

cycle and then exposed to hydrogen gas. After 4h, the mixture was filtered through celite and evaporated. The residue was purified by chromatography using 2% MeOH/CH_2Cl_2 as eluent to afford a gum (7mg).

Intermediate 18

Tert-butyl-2-[4-(2-(2-(4-morpholinylphenyl)-1-oxoethyl)aminoethyl) phenylthio]-2-methyl propionate

To a solution of Intermediate 4 (3.54 g, 12 mmol) and (4-morpholinylphenyl) acetic acid (3.1 g, 14 mmol) in CH_2Cl_2 (200 mL) was added 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrohloride (2.7 g;14 mmol). The mixture was stirred for 4 hr at 23 °C. After diluting with CH_2Cl_2 (200 mL), the solution was washed twice with water (100 mL), dried (Na_2SO_4), evaporated, and the residue purified by silica gel chromatography to yield a light tan-colored solid (4.5 g;75%). Mass Spectrum (ES^+) 499.1 (MH^+, 60%), 521.1 ($M+Na^+$, 100%); ^1H NMR ($CDCl_3$) δ 7.36 (d, 2H, J = 8.1 Hz), 7.05 (d, 2H, J = 8.6 Hz), 6.99 (d, 2H, J = 7.9 Hz), 6.84 (d, 2H, J = 8.5 Hz), 5.36 (br s, 1H), 3.87 (t, 4H, J=4.8 Hz), 3.45 (s, 2H), 3.42 (q, 2H, J = 6.4 Hz), 3.15 (t, 4H, J= 4.8 Hz), 2.72 (t, 2H, J = 7.0 Hz), 1.42 (s, 15H).

Intermediate 19

t-Butyl 2-(4-(2-(1-(2-(4-Morpholinophenyl)ethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionate

To a 0 °C THF (75 mL) solution of Intermediate 18 (3.88 g, 7.78 mmol) was added of 1M BH_3.THF complex in THF (54.4 mL; 54.4 mmol). The solution was allowed to stir for 5h while gradually warming to 23 °C. After cooling to 0 °C, MeOH (50 mL)was added dropwise and the solution was concentrated to dryness. The resulting oil was refluxed for 30 min with n-butanol (50 mL) in the presence of 4 mL (excess) of cyclohexylisocyanate. Upon cooling and concentration, the crude product was purified by silica gel chromatography using 20%-80% EtOAc in Hexanes as eluent to yield a colorless, viscous oil (2.8 g; 60%). Mass Spectrum (ES^+) 610.1 (MH^+, 60%), 632.1 ($M+Na^+$, 50%); ^1H NMR (d_6-DMSO) δ 7.33 (d, 2H, J=8.1 Hz), 7.18 (d,

2H, J=7.9 Hz), 7.02 (d, 2H, J=8.6 Hz), 6.82 (d, 2H, J=8.6 Hz), 5.63 (d, 1H, J=7.8 Hz), 3.69 (t, 4H, J=4.5 Hz), 3.4-3.2 (m, 5H plus water peak), 3.00 (t, 4H, J=4.5 Hz), 2.69 (t, 2H, J=7.2 Hz), 2.57 (t, 2H, J=7.2 Hz), 1.65 (m, 4H), 1.53 (d, 1H, J=12.7 Hz), 1.32 (s, 9H), 1.3 (s,9H), 1.2-1.0 (m, 5H).

Example 4

2-(4-(2-(1-(2-(4-Morpholinophenyl)ethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

To a solution of Intermediate 19 (2.75 g, 4.5 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added 60 mL of 1:1 TFA: CH_2Cl_2. The solution was stirred for 60 min, then warmed to 23°C and stirred an additional 60 min. After concentration to dryness, the crude product as a solution in MeOH/ CH_2Cl_2 was neutralized to pH = ~7 with NH_4OH/MeOH solution. The biphasic mixture was separated ,the aqueous phase washed with CH_2Cl_2 and the combined organics dried (Na_2SO_4) and concentrated. Silica gel chromatography eluting with CH_2Cl_2, then 1% -20% MeOH in CH_2Cl_2 gave a maroon-colored oil. A second flush through a short plug of silica gel with 10% MeOH in 1:1 EtOAc: CH_2Cl_2 removed most of the color to yield a light tan-colored foamy solid (2.05 g; 82%). Mass Spectrum (ES^+) 554.1 (MH^+, 100%), 576.1 ($M+Na^+$, 90%); ^1H NMR (d_6-DMSO) δ 7.33 (d, 2H, J=8.0 Hz), 7.18 (d, 2H, J=8.0 Hz), 7.04 (d, 2H, J=8.6 Hz), 6.82 (d, 2H, J=8.2 Hz), 5.63 (d, 1H, J=7.7 Hz), 3.7 (t, 4H, J=4.7 Hz), 3.3 (t, 2H, J=7.6 Hz), 3.23 (t, 2H, J=7.5 Hz), 3.00 (t, 4H, J=4.6 Hz), 2.69 (t, 2H, J=7.5 Hz), 2.58 (t, 2H, J=7.4 Hz), 1.66 (m, 4H), 1.54 (d, 1H, J=12.7 Hz), 1.31 (s, 6H), 1.2-1.0 (m, 5H).

Intermediate 20

t-Butyl N-Heptanoyl-2-(4-(2-aminoethyl)phenylthio)-2-methylpropionate

A solution of Intermediate 4 (297 mg; 1.006 mmole) and heptanoic acid (196 mg; 1.51 mmole) in CH_2Cl_2 (7 mL) was treated with HOBToH_2O (77 mg; 0.5 mmole) and diisopropylcarbodiimide (253 mg; 2.012 mmole) and the resulting solution stirred at 23°C for 15 h. The solution was washed with saturated $NaHCO_3$ solution, 1N HCl and brine and the organic layer was dried (Na_2SO_4) and evaporated. The

residue was purified by chromatography using 20% EtOAc-Hexane as eluent to afford a gum (241 mg). ^{1}H-NMR ($CDCl_3$) δ 7.37 (d, 2H, J=8.0 Hz), 7.07 (d, 2H, J=8.0 Hz), 5.35 (br s, 1H), 3.44 (m, 2H), 2.75 (t, 2H, J=7.0 Hz), 2.28 (t, 1H, J=7.5 Hz), 2.05 (t, 2H, J=7.7 Hz), 1.47-1.59 (m, 3H), 1.35 (m, 13H), 1.19 (m, 6H), 0.8 (m, 3H).

Intermediate 21

t-Butyl 2-(4-(2-(1-Heptyl-3-(2,4-difluorophenyl)ureido)ethyl)phenylthio)-2-methylpropionate

A solution of Intermediate 20 (241 mg; 0.592 mmole) in THF (5 mL) was treated with a 1M solution of borane in THF (4 mL; 4 mmole) and the mixture allowed to stand at 23°C for 15 h. Excess borane was destroyed by the careful addition of methanol and the resulting solution heated under reflux for 30 min. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (5 mL) and treated with 2,4-difluorophenylisocyanate (184 mg; 1.184 mmole) and allowed to stand at 23°C for 15 h. The mixture was washed with 2N HCl and the organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by chromatography using EtOAc-Hexane as eluent to afford an oil (270 mg). ^{1}H-NMR ($CDCl_3$) δ 8.03 (m, 1H), 7.44 (d, 2H, J=8.2 Hz), 7.18 (d, 2H, J=7.8 Hz), 6.83 (m, 2H), 6.34 (br s, 1H), 3.52 (t, 2H, J=7.5 Hz), 3.19 (t, 2H, J=7.8 Hz), 2.92 (t, 2H, J=7.5 Hz), 1.59 (m, 2H), 1.41 (m, 13H), 1.3 (m, 9H), 0.88 (m, 3H).

Example 5

2-(4-(2-(1-Heptyl-3-(2,4-difluorophenyl)ureido)ethyl)phenylthio)-2-methylpropionic acid

A solution of Intermediate 21 (270 mg; 0.506 mmole) in CH_2Cl_2 (3 mL) and TFA (3 mL) was allowed to stand at 23°C for 4 h. The solvent was evaporated to afford a semi-solid (240 mg). ^{1}H-NMR ($CDCl_3$) δ 7.99 (m, 1H), 7.45 (d, 2H, J=7.8 Hz), 7.20 (d, 2H, J=8.1 Hz), 6.82 (m, 2H), 6.34 (br s, 1H), 3.53 (t, 2H, J=7.5 Hz), 3.16 (t, 2H, J=7.6 Hz), 2.92 (t, 2H, J=7.4 Hz), 2.20 (br, 2H), 1.85 (br, 2H), 1.75-1.52 (m, 4H), 1.42 (s, 6H), 1.45-1.15 (m, 11H), 0.87 (t, 3H, J=6.8 Hz).

Binding Assay.

To generate a bacterial expression plasmid for the ligand binding domain of hPPAR alpha, cDNA encoding the hinge and ligand binding domains of hPPAR alpha (amino acids 167-468) was amplified by polymerase chain reaction and the amplified product inserted in frame into the pGEX-2T plasmid (Pharmacia). The amplified region of hPPAR alpha was sequence confirmed. GST-hPPAR alpha was expressed in BL21(DE3)plysS cells and extracts prepared by freeze-thawing the cells in Bacterial Lysis Buffer (10 mM Tris, pH 8.0, 250 mM KCl, 1 mM DTT, 1% Triton X-100) followed by centrifugation at 40,000 x g for 30 minutes. Glycerol was added to the bacterial extracts to a final concentration of 10%. Bacterial extracts were dialyzed extensively against Bacterial Lysis Buffer containing 10% glycerol. Binding assays included 50 µg of bacterial extracts (containing GST-hPPAR alpha), 60 nM Radioligand, and either 10 µM Cold Radioligand (or comparative example) or vehicle alone (0.1% DMSO, final concentration) in buffer containing 10 mM Tris (pH 8.0), 50 mM KCl, 10 mM DTT. Binding reactions were incubated at 4°C for 2-3 hr. Bound radioactivity was separated from free radioactivity by elution through 1 ml Sephadex G-25 protein desalting columns (Boehringer Mannheim). Bound radioactivity eluted in the column void volume and was quantitated by liquid scintillation counting.

Results (data represent the mean of assays performed in triplicate and are presented as dpm).

No competitor	140000
+ 10 µM Cold Radioligand	25000
Specific Binding	115000

Transfection Assay

Plasmids: GAL4-hPPAR alpha chimera and UAS-tk-SPAP reporters. The GAL4-hPPAR alpha and the GAL4-hPPAR gamma expression constructs contain the

translation initiation sequence and amino acids 1-76 of the glucocorticoid receptor fused to amino acids 1-147 of the yeast (S.crevisiae) transcription factor GAL4 in the pSG5 expression vector (Stratagene). Amino acids 167-468 of hPPAR alpha or amino acids 195-475 of hPPAR gamma were amplified by polymerase chain reaction (PCR) using vent polymerase (New England Biolabs) and inserted C-terminal to the GAL4 sequences. The UAS-tk-SPAP reporter contain 5 copies of the GAL4 binding site inserted into pG12-tk-SPAP (Berger et al, 1988).

Transfection assay: SPAP reporter. CV-1 cells were plated in DME medium supplemented with 10% delipidated fetal calf serum at a density of 2.4 $x10^4$ cells per well in a 96-well plate (Costar) 16-24 h before transfection. In general, 8.0 ng of reporter plasmid, 25.0 ng of β-galactosidase expression vector (pCH110, Pharamacia), and 2.0 ng of GAL4-hPPAR alpha or GAL4-hPPAR gamma expression vector were mixed with carrier DNA (pBluescript, Stratagene) to a total of 80 ng of DNA per well in a volume of 10ml optiMEM I medium (Life Technologies). To this, a second mix, containing 9.3 ml optiMEM I medium and 0.7 ml of LIPOFECTAMINE™ (Life Technologies), was added. After 30 min. an additional 80ml of optiMEM I medium were added and the combined mix was then applied to the cells. 16 h later the medium was exchanged to DME medium supplemented with 10% delipidated and heat inactivated fetal calf serum and the test compound at a concentration of 10^{-5}M. After incubation for 24 h, SPAP activity and β-galactosidase activity were measured by directly adding to the medium 200ml substrate mix (16mM o-nitrophenyl β-D-galactopyranoside (Sigma), 120mM fluorescein diphosphate (Molecular Probes), 0.16% Triton X-100, 160mM diethanolamine pH9, 44.8mM NaCl, and 0.8mM $MgCl_2$). Alternatively, alkaline phosphatse and β-galactosidase activities were measured separately using standard protocols. Briefly, cells were lysed by adding 25ml 0.5% Triton X-100 to the supernatant. To 40ml cell lysate, 200ml β-galactosidase substrate reagent (36mM o-nitrophenyl β-D-galactopyranoside, 1.25mM $MgCl_2$, 2.8mM NaCl, 4.4M β-mercaptoethanol) or 200ml alkaline phosphatase substrate reagent (2.5 mM p-nitrophenyl phosphate, 0.5 mM $MgCl_2$, 28 mM NaCl, 1 M diethanolamine pH 9.85) were added and incubated for 1

h. Alkaline phosphatase activity was expressed as percent maximal induction obtained for reference compound BRL49653, normalized to β-galactosidase activity which served as internal control standard for transfection efficiency. **References**; see, for example, Berger, J., et al., (1988), Gene 66, 1-10.

Each of the five Examples showed 50% activation of hPPAR alpha at concentrations of 10^{-5} M or less. These five examples also selectively activate PPAR alpha over PPAR gamma such that the activity ratio, as explained above, is at least 10. Examples 1, 2, and 3 had activity ratios greater than 100.

The following rodent data was produced using Example 5. The purpose of the experiment is to demonstrate that activators of PPAR alpha are useful for the treatment of obesity, and dyslipidemia.

Diet-Induced Model of Dyslipidemia

Zucker lean male rats and Zucker fa/fa female rats were randomized into 3 treatment groups. The randomization was based on serum triglyceride concentration after three months on the TEKLAD high fat diet. Dosing with Example 5 or the appropriate vehicle, by oral gavage, began after 4 months of high fat feeding. Plasma glucose, lactate, serum insulin and lipid concentrations were obtained weekly, beginning on day 7 through 48 after the initiation of therapy. Metabolic data from each treatment group was collected weekly. Dexascan determinations of body mass composition obtained after 4 months on the high fat diet served as baseline. Changes in body mass composition due to therapy were determined by repeat measurements at the end of the study.

Treatment Group A Vehicle dosed twice a day (approximately 8 am and 4 pm).

Treatment Group B Example 5 (0.1 mg/kg) dosed twice a day.

Treatment Group C Example 5 (0.3 mg/kg) dosed twice a day.

The results are summarized in the following two tables.

5

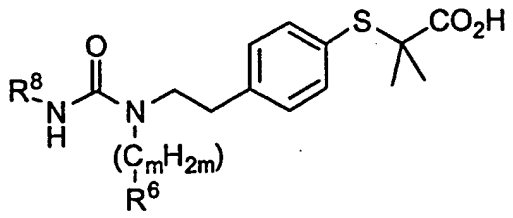
Males (n=4)	Group	After 4 months on high-fat diet	Week 1	Week 4	Week 7
		Control	Drug Treatment		
	Vehicle	788	718	741	725
Triglycerides (mg/dL)	0.1 mg/kg	828	460	467	584
	0.3 mg/kg	926	527	174	219
	Vehicle	227	191	224	215
Cholesterol (mg/dL)	0.1 mg/kg	221	138	189	148
	0.3 mg/kg	235	138	174	151
	Vehicle	0.67	0.85	0.65	0.60
NEFA (m Eq/L)	0.1 mg/kg	0.72	0.73	0.57	0.58
	0.3 mg/kg	0.72	0.69	0.47	0.46
	Vehicle	621	610	610	632
Body Weight (g)	0.1 mg/kg	636	617	592	597
	0.3 mg/kg	639	608	577	565

5

Females (n=4)	Group	After 4 months on high-fat diet	Week 1	Week 4	Week 7
		Control	Drug Treatment		
	Vehicle	8222	5357	10414	5465
Triglycerides (mg/dL)	0.1 mg/kg	9310	2717	3913	2627
	0.3 mg/kg	9190	1627	687	538
	Vehicle	1670	1186	1319	923
Cholesterol (mg/dL)	0.1 mg/kg	1648	610	733	632
	0.3 mg/kg	1908	350	404	422
	Vehicle	11.10	6.78	2.79	3.77
NEFA (m Eq/L)	0.1 mg/kg	11.15	2.47	1.32	1.75
	0.3 mg/kg	13.06	1.45	0.59	0.53
	Vehicle	649	684	700	706
Body Weight (g)	0.1 mg/kg	665	721	723	710
	0.3 mg/kg	645	673	643	582

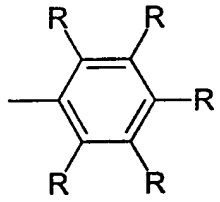
What is claimed is:

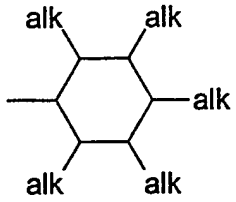
1. A compound of Formula (1), or an ester, salt, or physiologically functional derivative thereof

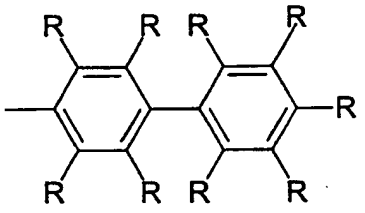


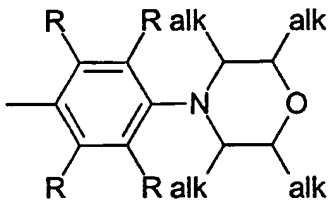
(1)

wherein m is from 0 to 20, R^6 is selected from the group consisting of hydrogen and

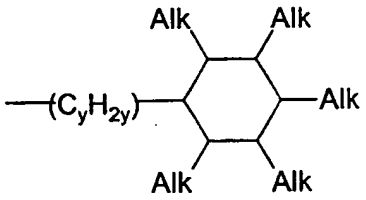


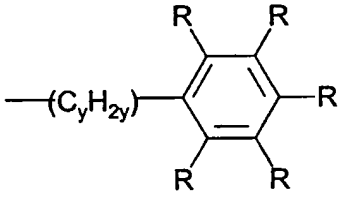






and R^8 is selected from the group consisting of





where y is 0, 1, or 2, each alk is independently hydrogen or alkyl group containing 1 to 6 carbon atoms, each R group is independently hydrogen,

halogen, cyano, $-NO_2$, phenyl, straight or branched alkyl or fluoroalkyl containing 1 to 6 carbon atoms and which can contain hetero atoms such as nitrogen, oxygen, or sulfur and which can contain functional groups such as ketone or ester, cycloalkyl containing 3 to 7 carbon atoms, or two R groups bonded to adjacent carbon atoms can, together with the carbon atoms to which they are bonded, form an aliphatic or aromatic ring or multi ring system, and where each depicted ring has no more than 3 alk groups or R groups that are not hydrogen.

2. The compound of Claim 1 wherein said compound is an activator of PPAR alpha.

3. The compound of Claim 1 wherein said compound is a selective activator of PPAR alpha.

4. The compound of any of Claims 1-3 wherein each R^6 and each R^8 has no more than 2 R groups and no more than 2 alk groups that are other than hydrogen.

5. The compound of any of Claims 1-4 Claim wherein y is 0, m is from 0 to 6, and each alk and each R group is hydrogen.

6. The compound of any of Claims 1-4 wherein said compound is

2-(4-(2-(1-(4-Biphenylethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

2-(4-(2-(1-(2-(4-Morpholinophenyl)ethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

2-(4-(2-(1-(Cyclohexanebutyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

2-(4-(2-(1-Heptyl-3-(2,4-difluorophenyl)ureido)ethyl)phenylthio)-2-methylpropionic acid

2-(4-(2-(1-(2-Chloro-4-(2-trifluoromethylphenyl) phenylmethyl)-3-(cyclohexyl)ureido)ethyl)phenylthio)-2-methylpropionic acid

or an ester, salt, or physiologically functional derivative thereof.

7. The compound of any of Claims 1-5 wherein said compound is

2-(4-(2-(1-(4-Biphenylethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

2-(4-(2-(1-(2-(4-Morpholinophenyl)ethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

2-(4-(2-(1-(Cyclohexanebutyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid

or an ester, salt, or physiologically functional derivative thereof.

8. A compound according to any of Claims 1-7 for use in therapy.

9. A pharmaceutical composition comprising a compound according to any of Claims 1-7.

10. A method for treating obesity or dyslipidemia comprising administration of a compound of any of Claims 1-7.

11. The method of Claim 10 wherein said compound is coadministered with an RXR ligand.

12. A method for treating a PPAR alpha mediated disease, risk factor, or condition comprising administering an effective amount of a compound of any of Claims 1-7.

13. The method of Claim 12 wherein said disease, risk factor, or condition is, or is associated with Alzheimer's disease, obesity, dyslipidemia, atherosclerosis, or diabetes.

14. Use of a compound according to any of Claims 1-7 for the manufacture of a medicament for the treatment of a PPAR alpha mediated disease, risk factor, or condition.

15. Use according to Claim 14 wherein the disease, risk factor, or condition is, or is associated with, Alzheimer's disease, obesity, dyslipidemia, atherosclerosis, or diabetes.

16. Use of a compound according to any of Claims 1-7 for the manufacture of a medicament for the treatment of obesity or dyslipidemia.

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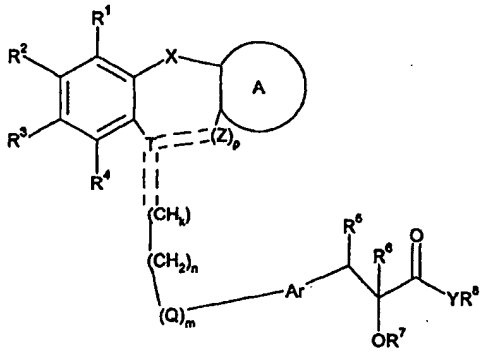

(I)

(57) Abstract

The present invention relates to compounds of general formula (I). The compounds are useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

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New Compounds, their Preparation and Use

FIELD OF INVENTION

The present invention relates to novel compounds, pharmaceutical compositions containing them, methods for preparing the compounds and their use as medicaments. More specifically, compounds of the invention can be utilised in the treatment of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

The present compounds reduce blood glucose and triglyceride levels and are accordingly useful for the treatment of ailments and disorders such as diabetes and obesity.

The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

The compounds are useful for the treatment and/or prophylaxis of insulin resistance (type 2 diabetes), impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, hyperglycaemia, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders. The compounds of the present invention are also useful for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis. These compounds may also be useful for improving cognitive functions in dementia, treating diabetic complications, psoriasis, polycystic ovarian syndrome (PCOS) and prevention and treatment of bone loss, e.g. osteoporosis.

BACKGROUND OF THE INVENTION

Coronary artery disease (CAD) is the major cause of death in type 2 diabetic and metabolic syndrome patients (i.e. patients that fall within the 'deadly quartet' category of impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

The hypolipidaemic fibrates and antidiabetic thiazolidinediones separately display moderately effective triglyceride-lowering activities although they are neither potent nor efficacious enough to be a single therapy of choice for the dyslipidaemia often observed in type 2 diabetic or metabolic syndrome patients. The thiazolidinediones also potently lower circulating glucose levels of type 2 diabetic animal models and humans. However, the fibrate class of compounds are without beneficial effects on glycaemia. Studies on the molecular actions of these compounds indicate that thiazolidinediones and fibrates exert their action by activating distinct transcription factors of the peroxisome proliferator activated receptor (PPAR) family, resulting in increased and decreased expression of specific enzymes and apolipoproteins respectively, both key-players in regulation of plasma triglyceride content. Fibrates, on the one hand, are PPARα activators, acting primarily in the liver. Thiazolidinediones, on the other hand, are high affinity ligands for PPARγ acting primarily on adipose tissue.

Adipose tissue plays a central role in lipid homeostasis and the maintenance of energy balance in vertebrates. Adipocytes store energy in the form of triglycerides during periods of nutritional affluence and release it in the form of free fatty acids at times of nutritional deprivation. The development of white adipose tissue is the result of a continuous differentiation process throughout life. Much evidence points to the central role of PPARγ activation in initiating and regulating this cell differentiation. Several highly specialised proteins are induced during adipocyte differentiation, most of them being involved in lipid storage and metabolism. The exact link from activation of PPARγ to changes in glucose metabolism, most notably a decrease in insulin resistance in muscle, has not yet been clarified. A possible link is via free fatty acids such that activation of PPARγ induces Lipoprotein Lipase (LPL), Fatty Acid Transport Protein (FATP) and Acyl-CoA Synthetase (ACS) in adipose tissue but not in muscle tissue. This, in turn, reduces the concentration of free fatty acids in plasma dramatically, and due to substrate competition at the cellular level, skeletal muscle and other tissues with high metabolic rates eventually switch from fatty acid oxidation to glucose oxidation with decreased insulin resistance as a consequence.

PPARα is involved in stimulating β-oxidation of fatty acids. In rodents, a PPARα-mediated change in the expression of genes involved in fatty acid metabolism lies at the basis of the phenomenon of peroxisome proliferation, a pleiotropic cellular response, mainly limited to liver and kidney and which can lead to hepatocarcinogenesis in rodents. The phenomenon

of peroxisome proliferation is not seen in man. In addition to its role in peroxisome proliferation in rodents, PPARα is also involved in the control of HDL cholesterol levels in rodents and humans. This effect is, at least partially, based on a PPARα-mediated transcriptional regulation of the major HDL apolipoproteins, apo A-I and apo A-II. The hypotriglyceridemic action of fibrates and fatty acids also involves PPARα and can be summarised as follows: (I) an increased lipolysis and clearance of remnant particles, due to changes in lipoprotein lipase and apo C-III levels, (II) a stimulation of cellular fatty acid uptake and their subsequent conversion to acyl-CoA derivatives by the induction of fatty acid binding protein and acyl-CoA synthase, (III) an induction of fatty acid b-oxidation pathways, (IV) a reduction in fatty acid and triglyceride synthesis, and finally (V) a decrease in VLDL production. Hence, both enhanced catabolism of triglyceride-rich particles as well as reduced secretion of VLDL particles constitutes mechanisms that contribute to the hypolipidemic effect of fibrates.

A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (U.S. Pat. 5,306,726, PCT Publications nos. W091/19702, WO 95/03038, WO 96/04260, WO 94/13650, WO 94/01420, WO 97/36579, WO 97/25042, WO 95/17394, WO 99/08501, WO 99/19313 and WO 99/16758).

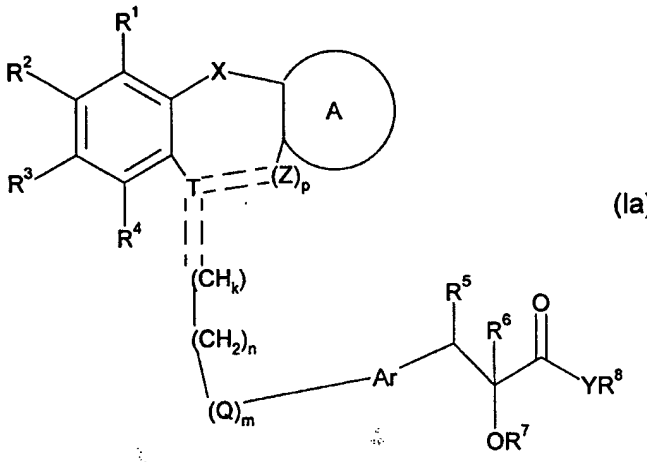
SUMMARY OF THE INVENTION

It seems more and more apparent that glucose lowering as a single approach does not overcome the macrovascular complications associated with type 2 diabetes and metabolic syndrome. Novel treatments of type 2 diabetes and metabolic syndrome must therefore aim at lowering both the overt hypertriglyceridaemia associated with these syndromes as well as alleviation of hyperglycaemia.

The clinical activity of fibrates and thiazolidinediones indicates that research for compounds displaying combined PPAR α and PPAR γ activation should lead to the discovery of efficacious glucose and triglyceride lowering drugs that have great potential in the treatment of type 2 diabetes and the metabolic syndrome (i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (Ia):



(Ia)

wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-12}alkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, halogen, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

or R^1 and R^2, R^2 and R^3 and/or R^3 and R^4 may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C_{1-6}alkyl;

ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy,

hydroxyC_{1-12}alkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, halogen, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

X is a valence bond, -(CHR^9)-, -(CHR^9)-CH_2-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH_2-, -(CHR^9)-CH=CH-, -(CHR^9)-CH_2-CH_2-, -(C=O)-, -O-CH_2-O-, -(NR^9)-, -(NR^9)-S(O_2)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH_2-(SO)-, -S-, -(SO)-, -(SO_2)-, -CH_2-(SO_2)-, -CH_2-O-CH_2-, wherein R^9 is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C_{1-12}alkyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{13}, or -SO_2R^{14}, wherein R^{13} and R^{14} independently of each other are selected from hydroxy, halogen, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl;

T is >N-, >CH-, >C<, -CH_2-N<;

Z is -CH_2-, =CH-, >N-, -O-, -S-, >CO, >SO, >SO_2, >NR^{11}, wherein R^{11} is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C_{1-12}alkyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{15}, or -SO_2R^{16}, wherein R^{15} and R^{16} independently of each other are selected from hydroxy, halogen, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl;

Q is -O-, -S-, $>SO_2$, $>NR^{12}$, wherein R^{12} is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C_{1-12}alkyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C_{1-12}alkylamino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{17}, or -SO_2R^{18}, wherein R^{17} and R^{18} independently of each other are selected from hydroxy, halogen, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl;

k is 1 or 2,

$T{=}{=}(Z)_p$ and $T{=}{=}(CH)_k$ independently of each other represents a single bond or a double bond, provided that both are not a double bond at the same time,

Ar represents arylene, heteroarylene, or a divalent heterocyclic group optionally substituted with one or more C_{1-6}alkyl or aryl;

R^5 represents hydrogen, hydroxy, halogen, C_{1-12}alkoxy, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R^5 forms a bond together with R^6,

R^6 represents hydrogen, hydroxy, halogen, C_{1-12}alkoxy, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, acyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R^6 forms a bond together with R^5,

R^7 represents hydrogen, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, aryl, aralkyl, C_{1-12}alkoxyC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, C_{1-12}alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

R^8 represents hydrogen, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

Y represents oxygen, sulphur or NR^{10}, where R^{10} represents hydrogen, C_{1-12}alkyl, aryl, hydroxyC_{1-12}alkyl or aralkyl groups or when Y is NR^{10}, R^8 and R^{10} may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C_{1-6}alkyl;

n is an integer ranging from 0 to 3;

m is an integer ranging from 0 to 1;

p is an integer ranging from 0 to 1;

with the proviso that T is not N when p is 0;

or a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, or cyano;
or R^1 and R^2, R^2 and R^3 and/or R^3 and R^4 may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C_{1-6}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, or C_{1-7}alkylthio.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, C_{1-7}alkyl, C_{1-7}alkoxy, aryl, or aryloxy.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, or C_{1-7}alkoxy.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, $-COR^{11}$, or $-SO_2R^{12}$, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, perhalomethyl, or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, or cyano.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, hydroxy, cyano, or C_{1-7}alkyl, C_{1-7}alkoxy.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(CHR^9)-CH=CH-, -(CHR^9)-CH$_2$-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-, -(NR^9)-S(O$_2$)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)-, -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen, halogen, hydroxy, cyano, C$_{1-7}$alkyl, C$_{1-7}$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C$_{1-7}$alkyl-amino, arylamino, aralkylamino, aminoC$_{1-7}$alkyl, C$_{1-7}$alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C$_{1-7}$alkoxyC$_{1-7}$alkyl, aryloxyC$_{1-7}$alkyl, aralkoxyC$_{1-7}$alkyl, C$_{1-7}$alkylthio, thioC$_{1-7}$alkyl, C$_{1-7}$alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{13}, or -SO$_2$R^{14}, wherein R^{13} and R^{14} independently of each other are selected from hydroxy, C$_{1-6}$alkoxy, amino optionally substituted with one or more C$_{1-6}$alkyl, perhalomethyl or aryl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(CHR^9)-CH=CH-, -(CHR^9)-CH$_2$-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-, -(NR^9)-S(O$_2$)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)-, -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen, halogen, hydroxy, C$_{1-7}$alkyl, C$_{1-7}$alkoxy, aryl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)-, -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen, halogen, hydroxy, C$_{1-7}$alkyl, C$_{1-7}$alkoxy, aryl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T is >N-, >CH- or >C<.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is -CH$_2$-, =CH-, >N-, -O-, -S-, >CO, >SO, >SO$_2$, >NR^{11}, wherein R^{11} is hydrogen, C$_{1-7}$alkyl, aryl, aralkyl, heterocyclyl, heteroaryl,

heteroaralkyl, acyl, acyloxy, hydroxyalkyl, aminoC_{1-7}alkyl, C_{1-7}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, thioC_{1-7}alkyl, -COR^{15}, or -SO_2R^{16}, wherein R^{15} and R^{16} independently of each other are selected from hydroxy, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is -CH_2-, =CH-, >N-, -O-, -S-, >CO, >SO, >SO_2, >NR^{11}, wherein R^{11} is hydrogen, C_{1-7}alkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is -CH_2-, =CH-, >N-, -O-, -S-, >CO, >SO, >SO_2, >NR^{11}, wherein R^{11} is hydrogen, C_{1-7}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is -O-, -S- or >NR^{12}, wherein R^{12} is hydrogen, or methyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene optionally substituted with one or more C_{1-6}alkyl or aryl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents phenyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^5 represents hydrogen, hydroxy, halogen, C_{1-7}alkoxy, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl or aralkyl, or R^5 forms a bond together with R^6.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^5 represents hydrogen or R^5 forms a bond together with R^6.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^6 represents hydrogen, C_{1-7}alkoxy, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, acyl or aralkyl, or R^6 forms a bond together with R^5.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^6 represents hydrogen or R^6 forms a bond together with R^5.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^7 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl, aralkyl, C_{1-7}alkoxyC_{1-7}alkyl, C_{1-7}alkoxycarbonyl, aryloxycarbonyl, C_{1-7}alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^7 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl or C_{2-7}-alkynyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^7 represents C_{1-2}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl or aralkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 represents hydrogen or C_{1-2}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen, sulphur or NR^{10}, where R^{10} represents hydrogen, C_{1-7}alkyl, aryl, hydroxyC_{1-7}alkyl or aralkyl groups.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A is benzo.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -O-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -S-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is $-(CHR^9)-CH_2-$, wherein R^9 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is $-O-(CHR^9)-$, wherein R^9 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is $-S-(CHR^9)-$, wherein R^9 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is $-(NR^9)-CH_2$, wherein R^9 is C_{1-12}-alkyl, preferably methyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is $-O-(CHR^9)-$, wherein R^9 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -(C=O)-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is $-(CHR^9)-$, wherein R^9 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is $-(CHR^9)-CH_2-CH_2-$, wherein R^9 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3 and R^4 are H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein n is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein n is 2.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein m is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein k is 0.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein k is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is -O-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein $T==(CH)_k$ represents a single bond or a double bond.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T is >CH- or >C<.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T is >N- and p is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is $-CH_2-$ or >CO and p is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^5 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^6 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^7 is ethyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 is ethyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is -S- and T is >CH-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is -O- and T is >CH-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar is phenylene.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein p is 0.

Preferred compounds of the invention are:

2-Ethoxy-3-[4-(2-xanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,

2-Methoxy-3-[4-(2-xanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-xanthen-9-ylidene-propoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-thioxanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,
2-Methoxy-3-[4-(2-thioxanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-thioxanthen-9-ylidene-propoxy)-phenyl]-propionic acid,
2-Ethoxy-3-{4-[2-(9*H*-thioxanthen-9-yl)-ethoxy]-phenyl}-propionic acid,
3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[2-(6*H*-Dibenzo[*b,e*]oxepin-11-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
2-Ethoxy-3-{4-[2-(11*H*-10-thia-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionic acid,
3-{4-[2-(5,11-Dihydro-10-thia-dibenzo[*a,d*]cyclohepten-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
2-Ethoxy-3-{4-[2-(5-methyl-5,6-dihydro-dibenzo[*b,e*]azepin-11-ylidene)-ethoxy]-phenyl}-propionic acid,
2-Ethoxy-3-{4-[2-(11-oxo-6,11-dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-propionic acid,
3-{4-[2-(6,11-Dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[2-(6,11-Dioxo-6,11-dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[2-(11*H*-Dibenzo[*b,f*][1,4]oxazepin-10-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[2-(11,12-Dihydro-dibenzo[*a,e*]cycloocten-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
Ethyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,
Propyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,
Butyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,
Pentyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,
Hexyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,
Heptyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,
N,N-Dimethyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,
N-Methyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,
N,N-Diethyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,
N-Ethyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,
N-Benzyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,

N-Propyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,
Ethyl 3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-2-methoxy-propionate,
Ethyl 3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-2-propoxy-propionate,
Ethyl 2-butoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-2-pentyloxy-propionate,
Ethyl 3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-2-hexyloxy-propionate,
Ethyl 3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-2-heptyloxy-propionate,
Ethyl 3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-2-methoxy-propionate,
Ethyl 2-ethoxy-3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-propionate,
Ethyl 3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-2-propoxy-propionate,
Ethyl 2-butoxy-3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-propionate,
Ethyl 3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-2-pentyloxy-propionate,
Ethyl 3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-2-hexyloxy-propionate,
Ethyl 3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-2-heptyloxy-propionate,
Ethyl 3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-2-methoxy-propionate,
Ethyl 2-ethoxy-3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-propionate,
Ethyl 3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-2-propoxy-propionate,
Ethyl 2-butoxy-3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-propionate,
Ethyl 3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-2-pentyloxy-propionate,
Ethyl 3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-2-hexyloxy-propionate,
Ethyl 3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-2-heptyloxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{2-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{2-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{2-butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{2-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{2-butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{3-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{3-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{3-butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{3-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{3-butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{4-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{4-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{4-butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,

Ethyl 2-ethoxy-3-[4-(2-{4-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{4-butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{3,6-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{2,7-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{4,5-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{3,6-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{2,7-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{4,5-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
3-[4-(2-Fluoren-9-ylidene-ethoxy)-phenyl]-2-methoxy-propionic acid,
2-Ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionic acid,
3-[4-(2-Fluoren-9-ylidene-ethoxy)-phenyl]-2-propoxy-propionic acid,
2-Butoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionic acid,
3-[4-(2-Fluoren-9-ylidene-ethoxy)-phenyl]-2-pentyloxy-propionic acid,
3-[4-(2-Fluoren-9-ylidene-ethoxy)-phenyl]-2-hexyloxy-propionic acid,
3-[4-(2-Fluoren-9-ylidene-ethoxy)-phenyl]-2-heptyloxy-propionic acid,
3-[4-(3-Fluoren-9-ylidene-propoxy)-phenyl]-2-methoxy-propionic acid,
2-Ethoxy-3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-propionic acid,
3-[4-(3-Fluoren-9-ylidene-propoxy)-phenyl]-2-propoxy-propionic acid,
2-Butoxy-3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-propionic acid,
3-[4-(3-Fluoren-9-ylidene-propoxy)-phenyl]-2-pentyloxy-propionic acid,
3-[4-(3-Fluoren-9-ylidene-propoxy)-phenyl]-2-hexyloxy-propionic acid,
3-[4-(3-Fluoren-9-ylidene-propoxy)-phenyl]-2-heptyloxy-propionic acid,
3-[4-(4-Fluoren-9-ylidene-butoxy)-phenyl]-2-methoxy-propionic acid,
2-Ethoxy-3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-propionic acid,
3-[4-(4-Fluoren-9-ylidene-butoxy)-phenyl]-2-propoxy-propionic acid
2-Butoxy-3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-propionic acid,
3-[4-(4-Fluoren-9-ylidene-butoxy)-phenyl]-2-pentyloxy-propionic acid,
3-[4-(4-Fluoren-9-ylidene-butoxy)-phenyl]-2-hexyloxy-propionic acid,
3-[4-(4-Fluoren-9-ylidene-butoxy)-phenyl]-2-heptyloxy-propionic acid,
2-Ethoxy-3-[4-(2-{2-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-{2-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
3-[4-(2-{2-Butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(2-{2-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
3-[4-(2-{2-Butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-{3-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-{3-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
3-[4-(2-{3-Butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(2-{3-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
3-[4-(2-{3-Butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(2-{4-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-{4-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
3-[4-(2-{4-Butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(2-{4-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
3-[4-(2-{4-Butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(2-{3,6-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-{2,7-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-{4,5-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-{3,6-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-{2,7-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-{4,5-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,
Ethyl 3-{4-[2-(6H-dibenzo[b,e]oxepin-11-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionate,
Ethyl 3-{4-[3-(6H-dibenzo[b,e]oxepin-11-ylidene)-propoxy]-phenyl}-2-ethoxy-propionate,
Ethyl 3-{4-[4-(6H-dibenzo[b,e]oxepin-11-ylidene)-butoxy]-phenyl}-2-ethoxy-propionate,
3-{4-[3-(6H-Dibenzo[b,e]oxepin-11-ylidene)-propoxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[4-(6H-Dibenzo[b,e]oxepin-11-ylidene)-butoxy]-phenyl}-2-ethoxy-propionic acid,
Ethyl 3-{4-[2-(6H-dibenzo[b,e]oxepin-11-ylidene)-ethoxy]-phenyl}-2-methoxy-propionate,
Ethyl 3-{4-[3-(6H-dibenzo[b,e]oxepin-11-ylidene)-propoxy]-phenyl}-2-methoxy-propionate,
Ethyl 3-{4-[4-(6H-dibenzo[b,e]oxepin-11-ylidene)-butoxy]-phenyl}-2-methoxy-propionate,
3-{4-[2-(6H-Dibenzo[b,e]oxepin-11-ylidene)-ethoxy]-phenyl}-2-methoxy-propionic acid,
3-{4-[3-(6H-Dibenzo[b,e]oxepin-11-ylidene)-propoxy]-phenyl}-2-methoxy-propionic acid,
3-{4-[4-(6H-Dibenzo[b,e]oxepin-11-ylidene)-butoxy]-phenyl}-2-methoxy-propionic acid,
Ethyl 3-{4-[2-(6H-dibenzo[b,e]oxepin-11-ylidene)-ethoxy]-phenyl}-2-propoxy-propionate,
Ethyl 3-{4-[3-(6H-dibenzo[b,e]oxepin-11-ylidene)-propoxy]-phenyl}-2-propoxy-propionate,
Ethyl 3-{4-[4-(6H-dibenzo[b,e]oxepin-11-ylidene)-butoxy]-phenyl}-2-propoxy-propionate,
3-{4-[2-(6H-Dibenzo[b,e]oxepin-11-ylidene)-ethoxy]-phenyl}-2-propoxy-propionic acid,
3-{4-[3-(6H-Dibenzo[b,e]oxepin-11-ylidene)-propoxy]-phenyl}-2-propoxy-propionic acid,
3-{4-[4-(6H-Dibenzo[b,e]oxepin-11-ylidene)-butoxy]-phenyl}-2-propoxy-propionic acid,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,

Propyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,

Butyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,

Pentyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,

Hexyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,

Heptyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,

N,*N*-Dimethyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,

N-Methyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,

N,*N*-Diethyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,

N-Ethyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,

N-Benzyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,

N-Propyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,

Ethyl 3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-2-methoxy-propionate,

Ethyl 3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-2-propoxy-propionate,

Ethyl 2-butoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-2-pentyloxy-propionate,

Ethyl 3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-2-hexyloxy-propionate,

Ethyl 3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-2-heptyloxy-propionate,

Ethyl 3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-2-methoxy-propionate,

Ethyl 2-ethoxy-3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-propionate,

Ethyl 3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-2-propoxy-propionate,

Ethyl 2-butoxy-3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-propionate,

Ethyl 3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-2-pentyloxy-propionate,

Ethyl 3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-2-hexyloxy-propionate,

Ethyl 3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-2-heptyloxy-propionate,

Ethyl 3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-2-methoxy-propionate,

Ethyl 2-ethoxy-3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-propionate,

Ethyl 3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-2-propoxy-propionate,

Ethyl 2-butoxy-3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-propionate,

Ethyl 3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-2-pentyloxy-propionate,

Ethyl 3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-2-hexyloxy-propionate,

Ethyl 3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-2-heptyloxy-propionate,

Ethyl 2-ethoxy-3-[4-(2-{9*H*-2-methoxyfluoren-9-yl)}-ethoxy)-phenyl]-propionate,

Ethyl 2-ethoxy-3-[4-(2-{9*H*-2-propoxyfluoren-9-yl)}-ethoxy)-phenyl]-propionate,

Ethyl 3-[4-(2-(9*H*-2-butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-2-methylfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-(9*H*-2-butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-3-methoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-3-propoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-(9*H*-3-butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-3-methylfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-(9*H*-3-butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-4-methoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-4-propoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-(9*H*-4-butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-4-methylfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-(9*H*-4-butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-3,6-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-2,7-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-4,5-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-3,6-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-2,7-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-4,5-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionate,
3-[4-(2-(9*H*-Fluoren-9-yl)-ethoxy)-phenyl]-2-methoxy-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-Fluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
3-[4-(2-(9*H*-Fluoren-9-yl)-ethoxy)-phenyl]-2-propoxy-propionic acid,
2-Butoxy-3-[4-(2-(9H-fluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
3-[4-(2-(9*H*-Fluoren-9-yl)-ethoxy)-phenyl]-2-pentyloxy-propionic acid,
3-[4-(2-(9*H*-Fluoren-9-yl)-ethoxy)-phenyl]-2-hexyloxy-propionic acid,
3-[4-(2-(9*H*-Fluoren-9-yl)-ethoxy)-phenyl]-2-heptyloxy-propionic acid,
3-[4-(3-(9*H*-Fluoren-9-yl)-propoxy)-phenyl]-2-methoxy-propionic acid,
2-Ethoxy-3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-propionic acid,
3-[4-(3-(9*H*-Fluoren-9-yl)-propoxy)-phenyl]-2-propoxy-propionic acid,
2-Butoxy-3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-propionic acid,
3-[4-(3-(9*H*-Fluoren-9-yl)-propoxy)-phenyl]-2-pentyloxy-propionic acid,
3-[4-(3-(9*H*-Fluoren-9-yl)-propoxy)-phenyl]-2-hexyloxy-propionic acid,
3-[4-(3-(9*H*-Fluoren-9-yl)-propoxy)-phenyl]-2-heptyloxy-propionic acid,
3-[4-(4-(9*H*-Fluoren-9-yl)-butoxy)-phenyl]-2-methoxy-propionic acid,
2-Ethoxy-3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-propionic acid,

3-[4-(4-(9*H*-Fluoren-9-yl)-butoxy)-phenyl]-2-propoxy-propionic acid,

2-Butoxy-3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-propionic acid,

3-[4-(4-(9*H*-Fluoren-9-yl)-butoxy)-phenyl]-2-pentyloxy-propionic acid,

3-[4-(4-(9*H*-Fluoren-9-yl)-butoxy)-phenyl]-2-hexyloxy-propionic acid,

3-[4-(4-(9*H*-Fluoren-9-yl)-butoxy)-phenyl]-2-heptyloxy-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-2-methoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-2-propoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

3-[4-(2-(9*H*-2-Butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-2-methylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

3-[4-(2-(9*H*-2-Butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-3-methoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-3-propoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

3-[4-(2-(9*H*-3-Butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-3-methylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

3-[4-(2-(9*H*-3-Butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-4-methoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-4-propoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

3-[4-(2-(9*H*-4-Butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-4-methylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

3-[4-(2-(9*H*-4-Butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-3,6-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-2,7-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-4,5-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-3,6-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-2,7-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-(9*H*-4,5-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

Ethyl 3-{4-[2-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionate,

Ethyl 3-{4-[3-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-ethoxy-propionate,

Ethyl 3-{4-[4-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-ethoxy-propionate,

3-{4-[3-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[4-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-ethoxy-propionic acid,

Ethyl 3-{4-[2-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-methoxy-propionate,

Ethyl 3-{4-[3-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-methoxy-propionate,

Ethyl 3-{4-[4-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-methoxy-propionate,

3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[3-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[4-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-methoxy-propionic acid,

Ethyl 3-{4-[2-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-propoxy-propionate,

Ethyl 3-{4-[3-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-propoxy-propionate,

Ethyl 3-{4-[4-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-propoxy-propionate,

3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-propoxy-propionic acid,

3-{4-[3-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-propoxy-propionic acid,

3-{4-[4-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-propoxy-propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yl)-ethoxy]-phenyl}-propionate,

Ethyl 2-ethoxy-3-{4-[3-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yl)-propoxy]-phenyl}-propionate,

Ethyl 2-ethoxy-3-{4-[4-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yl)-butoxy]-phenyl}-propionate,

2-Ethoxy-3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yl)-ethoxy]-phenyl}-propionic acid,

2-Ethoxy-3-{4-[3-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-propoxy]-phenyl}-propionic acid,

2-Ethoxy-3-{4-[4-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-butoxy]-phenyl}-propionic acid,

Ethyl 3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethoxy]-phenyl}-2-methoxy-propionate,

Ethyl 3-{4-[3-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-propoxy]-phenyl}-2-methoxy-propionate,

Ethyl 3-{4-[4-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-butoxy]-phenyl}-2-methoxy-propionate,

2-Methoxy-3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethoxy]-phenyl}-propionic acid,

2-Methoxy-3-{4-[3-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-propoxy]-phenyl}-propionic acid,

2-Methoxy-3-{4-[4-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-butoxy]-phenyl}-propionic acid,

Ethyl 3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethoxy]-phenyl}-2-propoxy-propionate,

Ethyl 3-{4-[3-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-propoxy]-phenyl}-2-propoxy-propionate,

Ethyl 3-{4-[4-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-butoxy]-phenyl}-2-propoxy-propionate,

3-{4-[2-(11*H*-5-Oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethoxy]-phenyl}-2-propoxy-propionic acid,

3-{4-[3-(11*H*-5-Oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-propoxy]-phenyl}-2-propoxy-propionic acid,

3-{4-[4-(11*H*-5-Oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-butoxy]-phenyl}-2-propoxy-propionic acid,

Ethyl 2-methoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionate,

2-Methoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionate,

2-Ethoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionic acid,

Ethyl 2-propoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionate,

2-Propoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionic acid,

Ethyl 2-methoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionate,
2-Methoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionic acid,
Ethyl 2-ethoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionate,
2-Ethoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionic acid,
Ethyl 2-propoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionate,
2-Propoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionic acid,
Ethyl 2-methoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionate,
2-Methoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionic acid,
Ethyl 2-ethoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionate,
2-Ethoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionic acid,
Ethyl 2-propoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionate,
2-Propoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionic acid,
Ethyl 3-(4-(2-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-methoxy-propionate,
3-(4-(2-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-methoxypropionic acid,
Ethyl 3-(4-(3-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-methoxy-propionate,
3-(4-(3-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-methoxypropionic acid,
Ethyl 3-(4-(4-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-methoxy-propionate,
3-(4-(4-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-methoxypropionic acid,
Ethyl 3-(4-(2-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-ethoxypropionate,
3-(4-(2-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-ethoxypropionic acid,
Ethyl 3-(4-(3-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-ethoxy-propionate,
3-(4-(3-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-ethoxypropionic acid,
Ethyl 3-(4-(4-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-ethoxypropionate,
3-(4-(4-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-ethoxypropionic acid,
Ethyl 3-(4-(2-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-propoxy-propionate,
3-(4-(2-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-propoxypropionic acid,
Ethyl 3-(4-(3-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-propoxy-propionate,

3-(4-(3-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-propoxypropionic acid,

Ethyl 3-(4-(4-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-propoxy-propionate,

3-(4-(4-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-propoxypropionic acid,

Ethyl 2-ethoxy-3-[4-(2-{indeno[2,1-*b*]pyridin-9-ylidene}-ethoxy)-phenyl]-propionate,

2-Ethoxy-3-[4-(2-{indeno[2,1-*b*]pyridin-9-ylidene}-ethoxy)-phenyl]-propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(9*H*-indeno[2,1-*b*]pyridin-9-yl)-ethoxy]-phenyl}-propionate,

2-Ethoxy-3-{4-[2-(9*H*-indeno[2,1-*b*]pyridin-9-yl)-ethoxy]-phenyl}-propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(1-oxa-cyclopenta[*a*]inden-8-ylidene)-ethoxy]-phenyl}-propionate,

2-Ethoxy-3-{4-[2-(1-oxa-cyclopenta[*a*]inden-8-ylidene)-ethoxy]-phenyl}-propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(8*H*-1-oxa-cyclopenta[*a*]inden-8-yl)-ethoxy]-phenyl}-propionate,

2-Ethoxy-3-{4-[2-(8*H*-1-oxa-cyclopenta[*a*]inden-8-yl)-ethoxy]-phenyl}-propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionate,

2-Ethoxy-3-{4-[2-(dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(10-methyldibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionate,

2-Ethoxy-3-{4-[2-(10-methyldibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(10-oxo-10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionate,

2-Ethoxy-3-{4-[2-(10-oxo-10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(10-methyl-10*H*-acridin-9-ylidene)-ethoxy]-phenyl}-propionate,

2-Ethoxy-3-{4-[2-(10-methyl-10*H*-acridin-9-ylidene)-ethoxy]-phenyl}-propionic acid,

Ethyl 3-{4-[2-(10*H*-acridin-9-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionate,

3-{4-[2-(10*H*-Acridin-9-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(10-oxo-10*H*-anthracen-9-ylidene)-ethoxy]-phenyl}-propionate,

2-Ethoxy-3-{4-[2-(10-oxo-10*H*-anthracen-9-ylidene)-ethoxy]-phenyl}-propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(9*H*-thioxanthen-9-yl)-ethoxy]-phenyl}-propionate,

Ethyl 2-ethoxy-3-{4-[2-(11*H*-10-thia-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionate;

or a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention are:

2-Ethoxy-3-[4-(2-xanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,

2-Methoxy-3-[4-(2-xanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-xanthen-9-ylidene-propoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-thioxanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,

2-Methoxy-3-[4-(2-thioxanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-thioxanthen-9-ylidene-propoxy)-phenyl]-propionic acid,

2-Ethoxy-3-{4-[2-(9*H*-thioxanthen-9-yl)-ethoxy]-phenyl}-propionic acid,

3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(6*H*-Dibenzo[*b,e*]oxepin-11-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

2-Ethoxy-3-{4-[2-(11*H*-10-thia-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionic acid,

3-{4-[2-(5,11-Dihydro-10-thia-dibenzo[*a,d*]cyclohepten-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

2-Ethoxy-3-{4-[2-(5-methyl-5,6-dihydro-dibenzo[*b,e*]azepin-11-ylidene)-ethoxy]-phenyl}-propionic acid,

2-Ethoxy-3-{4-[2-(11-oxo-6,11-dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-propionic acid,

3-{4-[2-(6,11-Dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(6,11-Dioxo-6,11-dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(11*H*-Dibenzo[*b,f*][1,4]oxazepin-10-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(11,12-Dihydro-dibenzo[*a,e*]cycloocten-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid;

or a pharmaceutically acceptable salt thereof.

In the above structural formulas and throughout the present specification, the following terms have the indicated meaning:

The terms "C_{1-12}-alkyl" as used herein, alone or in combination is intended to include those alkyl groups of the designated length in either a linear or branched or cyclic configuration. represents e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl

and the like. Typical C_{1-6}-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, hexyl, iso-hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

The terms "$C_{2-n'}$-alkenyl" wherein n' can be from 3 through 15, as used herein, represents an olefinically unsaturated branched or straight group having from 2 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-proppenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl, and the like.

The terms "$C_{2-n'}$-alkynyl" wherein n' can be from 3 through 15, as used herein, represent an unsaturated branched or straight group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl and the like.

The terms "$C_{4-n'}$-alkenynyl" wherein n' can be from 5 through 15, as used herein, represent an unsaturated branched or straight hydrocarbon group having from 4 to the specified number of carbon atoms and both at least one double bond and at least one triple bond. Examples of such groups include, but are not limited to, 1-penten-4-yne, 3-penten-1-yne, 1,3-hexadiene-5-yne and the like.

The term "C_{1-12}-alkoxy" as used herein, alone or in combination is intended to include those C_{1-12}-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked thorugh an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isoprpoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Example of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The term "C_{1-6}-alkoxycarbonyloxy" is intended to include the above defined C_{1-6}-alkoxy groups attached to a carbonyloxy moiety, eg. methoxycarbonyloxy, ethoxycarbonyloxy, etc..

As used herein the term "C_{4-12}-(cycloalkylalkyl)" represents a branched or straight alkyl group substituted at a carbon with a cycloalkyl group. Examples of such groups include, but are

not limited to, cyclopropylethyl, cyclobutylmethyl, 2-(cyclohexyl)ethyl, cyclohexylmethyl, 3-(cyclopentyl)-1-propyl, and the like.

The term "C_{1-12}-alkylthio" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C_{1-12}-alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 12 carbon atoms e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio. Example of cyclic alkylthio are cyclopropylthio, cyclobutylthio, cyclopentylthio and cyclohexylthio.

The term "C_{1-12}alkylamino" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C_{1-12}-alkyl group linked through amino having a free valence bond from the nitrogen atom e.g. methylamino, ethylamino, propylamino, butylamino, pentylamino. Example of cyclic alkylamino are cyclopropylamino, cyclobutylamino, cyclopentylamino and cyclohexylamino.

The term "hydroxyC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached a hydroxy group, e.g. hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl etc..

The term "arylamino" as used herein, alone or in combination, refers to an aryl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. phenylamino, naphthylamino, etc..

The term "aralkylamino" as used herein, alone or in combination, refers to an aralkyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. benzylamino, phenethylamino, 3-phenylpropylamino, 1-naphtylmethylamino, 2-(1-naphtyl)ethylamino and the like.

The term "aminoC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached an amino group, e.g. aminoethyl, 1-aminopropyl, 2-aminopropyl etc..

The term "aryloxycarbonyl" as used herein, alone or in combination, refers to an aryloxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. phenoxycarbonyl, 1-naphthyloxycarbonyl or 2-naphthyloxycarbonyl, etc..

The term "aralkoxycarbonyl" as used herein, alone or in combination, refers to an aralkoxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. benzyloxycarbonyl, phenethoxycarbonyl, 3-phenylpropoxycarbonyl, 1-naphthylmethoxycarbonyl, 2-(1-naphtyl)ethoxycarbonyl, etc..

The term "C_{1-12}alkoxyC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached a C_{1-12}alkoxy as defined herein, e.g. methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, etc..

The term "aryloxyC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached an aryloxy as defined herein, e.g. phenoxymethyl, phenoxydodecyl, 1-naphthyloxyethyl, 2-naphthyloxypropyl, etc..

The term "aralkoxyC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached an aralkoxy as defined herein, e.g. benzyloxymethyl, phenethoxydodecyl, 3-phenylpropoxyethyl, 1-naphthylmethoxypropyl, 2-(1-naphtyl)ethoxymethyl, etc..

The term "thioC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached a group of formula -SR"' wherein R"' is hydrogen, C_{1-6}alkyl or aryl, e.g. thiomethyl, methylthiomethyl, phenylthioethyl, etc..

The term "C_{1-12}alkoxycarbonylamino" as used herein, alone or in combination, refers to a C_{1-12}alkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. methoxycarbonylamino, carbethoxyamino, propoxycarbonylamino, isopropoxycarbonylamino, n-butoxycarbonylamino, tert-butoxycarbonylamino, etc..

The term "aryloxycarbonylamino" as used herein, alone or in combination, refers to an aryloxycarbonyl as defined herein linked through amino having a free valence bond from the

nitrogen atom e.g. phenoxycarbonylamino, 1-naphthyloxycarbonylamino or 2-naphthyloxycarbonylamino, etc..

The term "aralkoxycarbonylamino" as used herein, alone or in combination, refers to an aralkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. benzyloxycarbonylamino, phenethoxycarbonylamino, 3-phenylpropoxycarbonylamino, 1-naphthylmethoxycarbonylamino, 2-(1-naphtyl)ethoxycarbonylamino, etc..

The term "aryl" is intended to include aromatic rings, such as carboxylic aromatic rings selected from the group consisting of phenyl, naphthyl, (1-naphtyl or 2-naphtyl) optionally substituted with halogen, amino, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy.

The term "arylene" is intended to include divalent aromatic rings, such as carboxylic aromatic rings selected from the group consisting of phenylene, naphthylene, optionally substituted with halogen, amino, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "perhalomethyl" means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

The term "C_{1-6}-dialkylamino" as used herein refers to an amino group wherein the two hydrogen atoms independently are substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-pentyl)amino, and the like.

The term "acyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-alkyl group linked through a carbonyl group; such as e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl, and the like.

The term "acyloxy" as used herein refers to acyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy, valeryloxy, and the like.

The term "C_{1-12}-alkoxycarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-12}-alkoxy group linked through a carbonyl group; such as e.g. methoxycarbonyl, carbethoxy, propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 3-methylbutoxycarbonyl, n-hexoxycarbonyl and the like.

The term "a cyclic ring containing from 5 to 7 carbon atoms" as used herein refers to a monocyclic saturated or unsaturated or aromatic system, wherein the ring may be cyclopentyl, cyclopentenyl, cyclohexyl, phenyl or cycloheptyl.

The term "bicycloalkyl" as used herein refers to a monovalent substituent comprising a bicyclic structure made of 6-12 carbon atoms such as e.g. 2-norbornyl, 7-norbornyl, 2-bicyclo[2.2.2]octyl and 9-bicyclo[3.3.1]nonanyl.

The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine.

The term "heteroarylene" as used herein, alone or in combination, refers to a divalent group comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine.

The term "heteroaryloxy" as used herein, alone or in combination, refers to a heteroaryl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine linked to oxygen.

The term "aralkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphtylmethyl, 2-(1-naphtyl)ethyl and the like.

The term "aryloxy" as used herein refers to phenoxy, 1-naphthyloxy or 2-naphthyloxy.

The term "aralkoxy" as used herein refers to a C_{1-6}-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphtyl)ethoxy and the like.

The term "heteroaralkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with a heteroaryl group; such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like.

The term "heteroaralkoxy" as used herein refers to a heteroaralkyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom, e.g. (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl linked to oxygen.

The term "C_{1-6}-alkylsulfonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-alkyl group linked through a sulfonyl group such as e.g. methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, n-hexylsulfonyl, 4-methylpentylsulfonyl, neopentylsulfonyl, n-hexylsulfonyl and 2,2-dimethylpropylsulfonyl.

The term "C_{1-6}-monoalkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-monoalkylamino group linked through a sulfonyl group such as e.g.

methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, isopropylaminosulfonyl, n-butylaminosulfonyl, sec-butylaminosulfonyl, isobutylaminosulfonyl, tert-butylaminosulfonyl, n-pentylaminosulfonyl, 2-methylbutylaminosulfonyl, 3-methylbutylaminosulfonyl, n-hexylaminosulfonyl, 4-methylpentylaminosulfonyl, neopentylaminosulfonyl, n-hexylaminosulfonyl and 2,2-dimethylpropylaminosulfonyl.

The term "C_{1-6}-dialkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-dialkylamino group linked through a sulfonyl group such as dimethylaminosulfonyl, N-ethyl-N-methylaminosulfonyl, diethylaminosulfonyl, dipropylaminosulfonyl, N-(n-butyl)-N-methylaminosulfonyl, di(n-pentyl)aminosulfonyl, and the like.

The term "C_{1-6}-alkylsulfinyl" as used herein refers to a monovalent substituent comprising a straight or branched C_{1-6}-alkyl group linked through a sulfinyl group (-S(=O)-); such as e.g. methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl, and the like.

The term "acylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with an acyl group, such as e.g. acetamido, propionamido, isopropylcarbonylamino, and the like.

The term "(C_{3-6}-cycloalkyl)C_{1-6}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms and being monosubstituted with a C_{3-6}-cycloalkyl group, the cycloalkyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. cyclopropylmethyl, (1-methylcyclopropyl)methyl, 1-(cyclopropyl)ethyl, cyclopentylmethyl, cyclohexylmethyl, and the like.

The term "arylthio" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; e.g. phenylthio, (4-methylphenyl)- thio, (2-chlorophenyl)thio, and the like.

The term "arylsulfinyl" as used herein refers to an aryl group linked through a sulfinyl group (-S(=O)-), the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. phenylsulfinyl, (4-chlorophenyl)sulfinyl, and the like.

The term "arylsulfonyl" as used herein refers to an aryl group linked through a sulfonyl group, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. phenylsulfonyl, tosyl, and the like.

The term "C_{1-6}-monoalkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-monoalkylamino group linked through a carbonyl group such as e.g. methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl, sec-butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, 2-methylbutylaminocarbonyl, 3-methylbutylaminocarbonyl, n-hexylaminocarbonyl, 4-methylpentylaminocarbonyl, neopentylaminocarbonyl, n-hexylaminocarbonyl and 2-2-dimethylpropylaminocarbonyl.

The term "C_{1-6}-dialkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-dialkylamino group linked through a carbonyl group such as dimethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, N-(n-butyl)-N-methylaminocarbonyl, di(n-pentyl)aminocarbonyl, and the like.

The term "C_{1-6}-monoalkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C_{1-6}-monoalkylaminocarbonyl group, e.g. methylaminocarbonylamino, ethylamino-carbonylamino, n-propylaminocarbonylamino, isopropylaminocarbonylamino, n-butylaminocarbonylamino, sec-butylaminocarbonylamino, isobutylaminocarbonylamino, tert-butylaminocarbonylamino, and 2-methylbutylaminocarbonylamino.

The term "C_{1-6}-dialkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C_{1-6}-dialkylaminocarbonyl group, such as dimethylaminocarbonylamino, N-ethyl-N-methylaminocarbonylamino, diethylaminocarbonylamino, dipropylaminocarbonylamino, N-(n-butyl)-N-methylaminocarbonylamino, di(n-pentyl)aminocarbonylamino, and the like.

As used herein, the phrase "heterocyclyl" means a monovalent saturated or unsaturated group being monocyclic and containing one or more, such as from one to four carbon atom(s), and from one to four N, O or S atom(s) or a combination thereof. The phrase "heterocyclyl" includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. pyrrolidine, pyrroline); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofurazan); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms.

As used herein, the phrase "a divalent heterocyclic group" means a divalent saturated or unsaturated system being monocyclic and containing one or more, such as from one to four carbon atom(s), and one to four N, O or S atom(s) or a combination thereof. The phrase a divalent heterocyclic group includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. pyrrolidine, pyrroline); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofurazan); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms.

As used herein, the phrase "a 5-6 membered cyclic ring" means an unsaturated or saturated or aromatic system containing one or more carbon atoms and optionally from one to four N, O or S atom(s) or a combination thereof. The phrase "a 5-6 membered cyclic ring" includes, but is not limited to, e.g. cyclopentyl, cyclohexyl, phenyl, cyclohexenyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiomorpholinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl, 1,4-dioxolanyl, 5-membered heterocycles having one hetero atom (e.g. thiophenes, pyrroles, furans); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g.

oxazoles, pyrazoles, imidazoles, thiazoles, purines); 5-membered heterocycles having three heteroatoms (e.g. triazoles, thiadiazoles); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. pyridine, quinoline, isoquinoline, phenanthridine, cyclohepta[b]pyridine); 6-membered heterocycles with two heteroatoms (e.g. pyridazines, cinnolines, phthalazines, pyrazines, pyrimidines, quinazolines, morpholines); 6-membered heterocycles with three heteroatoms (e.g. 1,3,5-triazine); and 6-membered heterocycles with four heteroatoms.

As used herein, the phrase "5- or 6-membered nitrogen containing ring" refers to a monovalent substituent comprising a monocyclic unsaturated or saturated or aromatic system containing one or more carbon, nitrogen, oxygen or sulfur atoms or a combination thereof and having 5 or 6 members, e.g. pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiomorpholinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl and 1,4-dioxolanyl.

Certain of the above defined terms may occur more than once in the above formula (Ia), and upon such occurence each term shall be defined independently of the other.

Pharmaceutically acceptable salts forming part of this invention include salts of the carboxylic acid moiety such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulplionates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula (Ia) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents lilke ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of

solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guandine and their derivatives etc. may also be used. Alternatively, acid addition salts whereever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

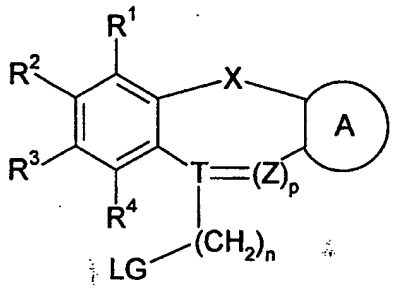
The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (Ia) may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (Ia) may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of compound of general formula (Ia) forming part of this invention may be prepared by crystallization of compound of formula (Ia) under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The invention also relates to a method of preparing the above mentioned compounds.

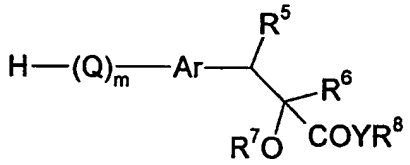
A compound of formula (Ia) can be prepared as described below:

By carrying out an alkylation reaction between a compound of formula I, wherein A, n, p, R^1, R^2, R^3, R^4, T, X and Z are as defined previously, and LG is a leaving group preferentially chosen from bromide, iodide, methanesulfonate, or 4-toluenesulfonate,



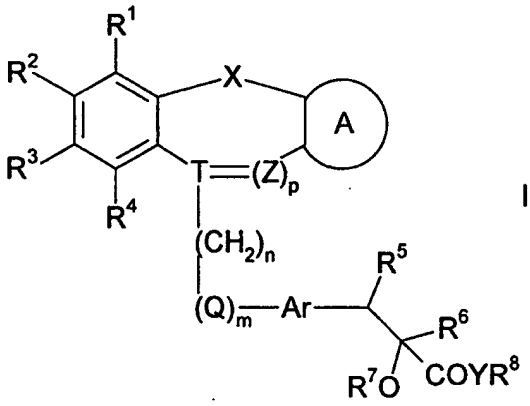
I

and a nucleophilic compound of formula II, wherein Ar, m, Q, R^5, R^6, R^7, R^8, and Y are as defined previously,



II

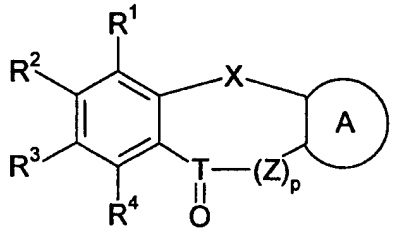
in the presence of a suitable base such as sodium or potassium carbonate, to give a product of formula III, wherein A, Ar, m, n, p, Q, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, T, X , Y and Z are as defined previously.



III

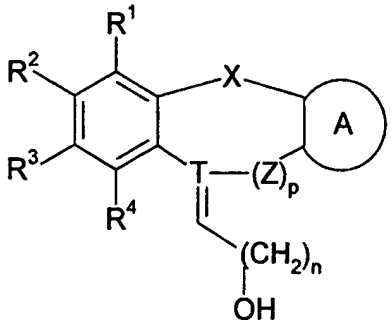
Alternatively, by joining a compound of formula I, wherein LG is an alcohol OH group, with a compound of formula II under Mitsunobu conditions, to give a product of formula III, wherein A, Ar, m, n, p, Q, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, T, X , Y and Z are as defined previously.

Alternatively, a compound of formula IV, wherein A, n, p, R^1, R^2, R^3, R^4, T, X and Z are as defined previously,



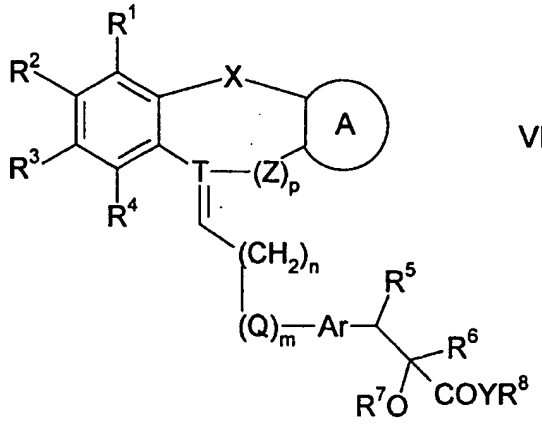
IV

may be reacted through a Wittig process with $(Ph_3P)_3P(CH_2)_{n+1}OH.Br$ in the presence of a suitable base such as butyllithium, to give compounds of formula V.



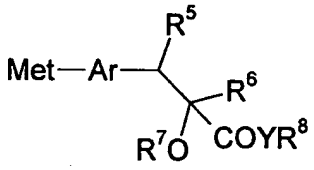
V

Compounds of formula V may then be reacted with compounds of formula II under Mitsunobu conditions to give compounds of formula VI, wherein A, Ar, m, n, p, Q, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, T, X , Y and Z are as defined previously.



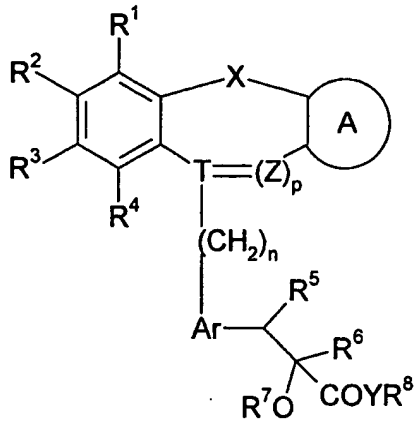
VI

Alternatively, a compound of formula I may be reacted, possibly under transition metal catalysis, with a nucleophilic compound of formula VII,



VII

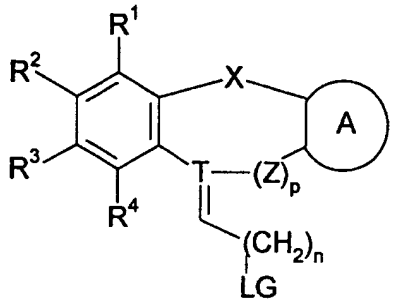
wherein "Met" is a metal such as zinc or copper, carrying suitable ligands chosen preferentially from trifluoro-methanesulfonate, halide or C_1-C_6 alkyl, and Ar, R^5, R^6, R^7, R^8, and Y are as defined previously, giving rise to products of formula VIII,



VIII

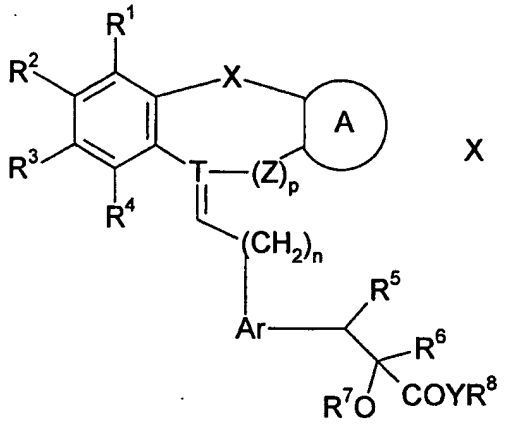
wherein A, Ar, n, p, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, T, X , Y and Z are as defined previously.

Alternatively, a nucleophilic compound of formula VII, wherein "Met" is as defined previously, may be reacted with an electrophilic compound of formula IX,



IX

giving rise to products of general formula X,



wherein A, Ar, n, p, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, T, X , Y and Z are as defined previously.

Compounds of formula III, VI, VIII and X are all belonging to the compounds of formula (Ia).

PHARMACOLOGICAL METHODS

In vitro PPAR alpha and PPAR gamma activation activity.

Principle

The PPAR gene transcription activation assays were based on transient transfection into human HEK293 cells of two plasmids encoding a chimeric test protein and a reporter protein respectively. The chimeric test protein was a fusion of the DNA binding domain (DBD) from the yeast GAL4 transcription factor to the ligand binding domain (LBD) of the human PPAR proteins. The PPAR LBD harbored in addition to the ligand binding pocket also the native activation domain (activating function 2 = AF2) allowing the fusion protein to function as a PPAR ligand dependent transcription factor. The GAL4 DBD will force the fusion protein to bind only to Gal4 enhancers (of which none existed in HEK293 cells). The reporter plasmid contained a Gal4 enhancer driving the expression of the firefly luciferase protein. After transfection, HEK293 cells expressed the GAL4-DBD-PPAR-LBD fusion protein. The fusion protein will in turn bind to the Gal4 enhancer controlling the luciferase expression, and do nothing in the absence of ligand. Upon addition to the cells of a PPAR ligand, luciferase

protein will be produced in amounts corresponding to the activation of the PPAR protein. The amount of luciferase protein is measured by light emission after addition of the appropriate substrate.

Methods

Cell culture and transfection: HEK293 cells were grown in DMEM + 10% FCS, 1% PS. Cells were seeded in 96-well plates the day before transfection to give a confluency of 80 % at transfection. 0,8 µg DNA per well was transfected using FuGene transfection reagent according to the manufacturers instructions (Boehringer-Mannheim). Cells were allowed to express protein for 48 h followed by addition of compound.

Plasmids: Human PPAR α and γ was obtained by PCR amplification using cDNA templates from liver, intestine and adipose tissue respectively. Amplified cDNAs were cloned into pCR2.1 and sequenced. The LBD from each isoform PPAR was generated by PCR (PPARα: aa 167 - C-term; PPARγ: aa 165 - C-term) and fused to GAL4-DBD by subcloning fragments in frame into the vector pM1 generating the plasmids pM1αLBD and pM1γLBD. Ensuing fusions were verified by sequencing. The reporter was constructed by inserting an oligonucleotide encoding five repeats of the Gal4 recognition sequence into the pGL2 vector (Promega).

Compounds: All compounds were dissolved in DMSO and diluted 1:1000 upon addition to the cells. Cells were treated with compound (1:1000 in 200 µl growth medium including delipidated serum) for 24 h followed by luciferase assay.

Luciferase assay: Medium including test compound was aspirated and 100 µl PBS incl. 1mM Mg++ and Ca++ was added to each well. The luciferase assay was performed using the LucLite kit according to the manufacturers instructions (Packard Instruments). Light emission was quantified by counting SPC mode on a Packard Instruments top-counter.

PHARMACEUTICAL COMPOSITIONS

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the general formula (Ia) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of formula (Ia) or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula (Ia) dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	5 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	Ad.
Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases related to the regulation of blood sugar.
Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a dosage of from about 2 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.001 mg to about 100 mg, preferably from about 0.01 mg to about 50 mg of the compounds of formula (Ia) admixed with a pharmaceutically acceptable carrier or diluent.

In a further aspect, the present invention relates to a method of treating and/or preventing type I or type II diabetes.

In a still further aspect, the present invention relates to the use of one or more compounds of the general formula (Ia) or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment and/or prevention of type I or type II diabetes.

Any novel feature or combination of features described herein is considered essential to this invention.

EXAMPLES

The process for preparing compounds of formula Ia, and preparations containing them is further illustrated in the following examples, which however, are not to be construed as limiting.

The structures of the compounds are confirmed by either elemental analysis (MA), proton nuclear magnetic resonance (^{1}H NMR) or mass spectrometry (MS). NMR shifts (δ) are quoted in parts per million (ppm) relative to tetramethylsilane and the signals are quoted showing number of protons in the integration, multiplicity, and coupling constants. Mp indicates melting point and is given in °C. Column chromatography was carried out using the method described by W.C. Still et al, J. Org. Chem. 1978, 43, 2923-2925 on Macherey Nagel 0.04-0.063 mm silica gel 60 (Art. 815380). Compounds used as starting materials are either known compounds or compounds which can be readily prepared by known methods.

Abbreviations:

TLC: Thin Layer Chromatography

DMSO: dimethylsulfoxide

$CDCl_3$: deuterated chloroform

min: minutes

h: hours

ml: millilitres

THF: Tetrahydrofuran

Et_2O; diethyl ether

Na_2SO_4: anhydrous sodium sulfate

$MgSO_4$: anhydrous magnesium sulfate

s: singlet

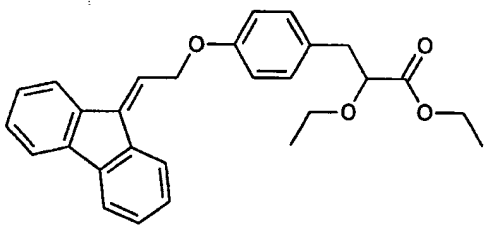
d: doublet

t: triplet

q: quartet

M^+: Molecular ion

EXAMPLE 1



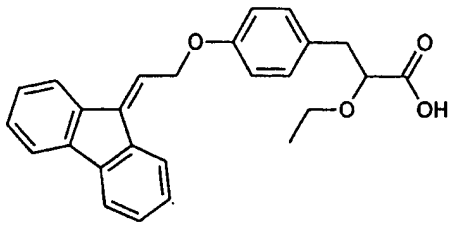
Ethyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate

Diethyl azodicarboxylate (0.235 ml, 1.49 mmol) was added at 0°C to a stirred solution of triphenylphosphine (0.392 g, 1.49 mmol) and 2-fluoren-9-ylidene-ethanol (0.208 g, 1.0 mmol) in dry THF (5 ml) and the mixture stirred for 5 min. A solution of ethyl 2-ethoxy-3-(4-hydroxy-phenyl)-propionate (0.356 g, 1.49 mmol) in dry THF (5 ml) was then added, the mixture allowed to warm to room temperature, and stirring continued for 72h. The resulting mixture was treated with water (50 ml), and the products extracted into dichloromethane (3 x 20 ml). The extracts were combined, washed with brine, dried (Na_2SO_4) and evaporated to a yellow gum. This was then purified by column chromatography on silica gel (15% Et_2O in petroleum eluent) to give ethyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate as a yellow gum; 0.28 g (60%).

^1H NMR (300MHz, $CDCl_3$) δ: 1.17 (3H, t, 7 Hz), 1.22 (3H, t, 7 Hz), 2.97 (2H, d, 7 Hz), 3.29-3.40 (1H, m), 3.54-3.66 (1H, m), 3.98 (1H, t, 7 Hz), 4.17 (2H, q, 7 Hz), 5.32 (2H, d, 6 Hz),

6.87 (1H, t, 6 Hz), 6.92 (2H, d, 8 Hz), 7.18 (2H, d, 8 Hz), 7.22-7.45 (4H, m), 7.57-7.77 (4H, m). MS: 428 (M^+), 382, 191 (100%).

EXAMPLE 2

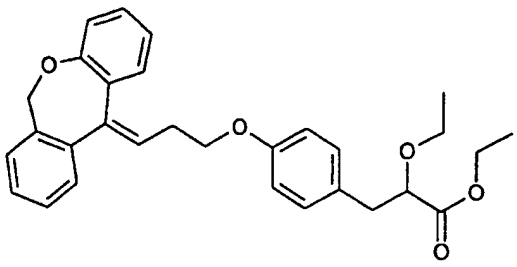


2-Ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionic acid

Lithium hydroxide (1M, 1.0 ml, 1.0 mmol) was added to a suspension of ethyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate (0.214 g, 0.5 mmol) in ethanol (5 ml) and the resulting mixture heated to gentle reflux for 30 min. The cooled mixture was partitioned between water (30 ml) and dichloromethane (20 ml), acidified to pH 1 by adding 1N hydrochloric acid (3 ml), and the organic phase collected. The aqueous phase was further extracted with dichloromethane (3 x 20 ml) and the combined organics were washed with brine, dried ($MgSO_4$) and evaporated to give a yellow gum. The product was purified by column chromatography on silica gel (3% methanol in dichloromethane eluent) to give 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionic acid, as a yellow solid; 0.104 g (51%).

^1H NMR (200MHz, $CDCl_3$) δ: 1.17 (3H, t, 7 Hz), 2.98 (1H, dd, 14 & 7 Hz), 3.10 (1H, dd, 14 & 4 Hz), 3.40-3.70 (2H, m), 4.06 (1H, dd, 7 & 4 Hz), 5.33 (2H, d, 6 Hz), 6.87 (1H, t, 6 Hz), 6.98 (2H, d, 8 Hz), 7.20 (2H, d, 8 Hz), 7.20-7.47 (4H, m), 7.55-7.80 (4H, m). MS: 400 (M^+), 435, 297, 235, 209, 191 (100%), 165.

EXAMPLE 3

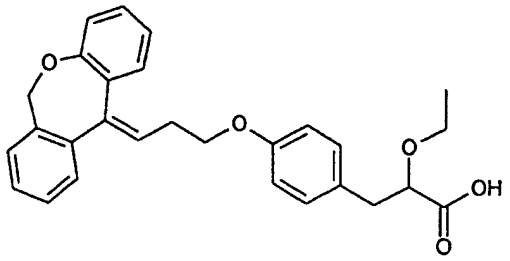


Ethyl 3-{4-[3-(6*H*-dibenzo[*b,e*]oxepin-11-ylidene)-propoxy]-phenyl}-2-ethoxy-propionate

Diethyl azodicarboxylate (0.235 ml, 1.49 mmol) was added at 0°C to a stirred solution of triphenylphosphine (0.392 g, 1.49 mmol) and 3-(6*H*-dibenzo[*b,e*]oxepin-11-ylidene)-1-propanol (0.252 g, 1.0 mmol) in dry THF (5 ml) and the mixture stirred for 5 min. A solution of ethyl 2-ethoxy-3-(4-hydroxyphenyl)-propionate (0.356 g, 1.49 mmol) in dry THF (5 ml) was then added, the mixture allowed to warm to room temperature, and stirring continued for 18h. The resulting mixture was treated with water (50 ml), and the products extracted into dichloromethane (4 x 50 ml). The extracts were combined, washed with brine, dried (Na_2SO_4) and evaporated to an orange gum. This was then purified by column chromatography on silica gel (20% Et_2O in petroleum eluent) to give the title compound as an inseparable 4:1 mixture of *E* and *Z* double-bond isomers, as a pale yellow gum; 0.252 g (53%).

^1H NMR (300MHz, $CDCl_3$) δ: 1.16 (3H, t, 7 Hz), 1.23 (3H, t, 7 Hz), 2.65 (1.6H, q, 7 Hz, *E* isomer), 2.90 (0.4H, q, 7 Hz, *Z* isomer), 2.94 (2H, d, 7 Hz), 3.29-3.40 (1H, m), 3.53-3.67 (1H, m), 3.97 (1H, t, 7 Hz), 4.01 (1.6H, t, 7 Hz, *E* isomer), 4.08 (0.4H, t, 7 Hz, *Z* isomer), 4.17 (2H, t, 7 Hz), 4.5-5.7 (2H, very broad m), 5.82 (0.2H, t, 7 Hz, *Z* isomer), 6.12 (0.8H, t, 7 Hz, *E* isomer), 6.75-.90 (4H, m), 7.1-7.4 (8H, m). MS: 472 (M^+), 426, 341, 326, 235 (100%), 221, 195, 107, 91.

EXAMPLE 4



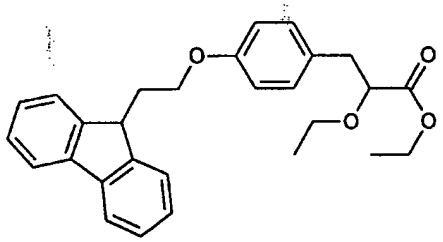
3-{4-[3-(6*H*-Dibenzo[*b,e*]oxepin-11-ylidene)-propoxy]-phenyl}-2-ethoxy-propionic acid

Sodium hydroxide (1M, 2.5 ml, 2.5 mmol) was added to a solution of a 4:1 *E/Z* double-bond isomer mixture of ethyl 3-{4-[3-(6*H*-dibenzo[*b,e*]oxepin-11-ylidene)-propoxy]-phenyl}-2-ethoxy-propionate (0.24 g, 0.51 mmol) in ethanol (5 ml) and the mixture stirred at room temperature for 78h. The resulting mixture was partitioned between 1N hydrochloric acid (20

ml) and dichloromethane (20 ml), and the organic phase collected. The aqueous phase was further extracted with dichloromethane (3 x 20 ml) and the combined organics washed with brine, dried (Na_2SO_4) and evaporated to give a pale yellow gum. This was then purified by column chromatography on silica gel (3% methanol in dichloromethane eluent) to give the title compound as an inseparable 4:1 mixture of *E* and *Z* double-bond isomers, as a pale yellow glass; 0.186 g (80%).

^{1}H NMR (200MHz, $CDCl_3$) δ: 1.16 (3H, t, 7), 2.65 (1.6H, q, 7, *E* isomer), 2.90 (0.4H, q, 7, *Z* isomer), 2.93 (1H, dd, 14 & 9), 3.05 (1H, dd, 14 &5), 3.32-3.70 (2H, m), 3.94-4.10 (3H, m), 4.5-5.7 (2H, very broad m), 5.80 (0.25H, t, 7, *Z* isomer), 6.12 (0.75H, t, 7, *E* isomer), 6.7-6.95 (4H, m), 7.05-7.20 (2H, m), 7.20-7.40 (6H, m). MS: 444 (M^+), 341, 326, 235 (100%), 221, 195, 107, 91.

EXAMPLE 5

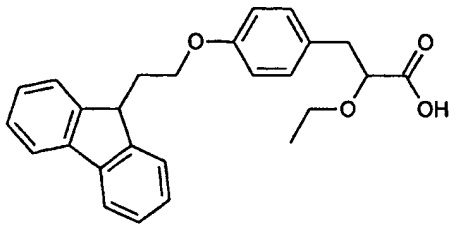


Ethyl 2-ethoxy-3-{4-[2-(9*H*-fluoren-9-yl)-ethoxy]-phenyl}-propionate

Diethyl azodicarboxylate (0.235 ml, 1.49 mmol) was added at 0°C to a stirred solution of triphenylphosphine (0.392 g, 1.49 mmol) and 2-(9*H*-fluoren-9-yl)-ethanol (0.208 g, 1.0 mmol) in dry THF (5 ml) and the mixture stirred for 5 min. A solution of ethyl 2-ethoxy-3-(4-hydroxy-phenyl)-propionate (0.356 g, 1.49 mmol) in dry THF (5 ml) was then added, the mixture allowed to warm to room temperature and stirring continued for 20h. The resulting mixture was treated with water (50 ml), and the products extracted into dichloromethane (4 x 50 ml). The extracts were combined, washed with brine, dried (Na_2SO_4) and evaporated to a colourless gum. This was then purified by column chromatography on SiO_2 (15% Et_2O in petroleum eluent) to give the title compound as a colourless gum; 0.20 g (47%).

^{1}H NMR (300MHz, $CDCl_3$) δ: 1.17 (3H, t, 7), 1.22 (3H, t, 7), 2.46 (2H, q, 7), 2.93 (2H, d, 7), 3.28-3.40 (1H, m), 3.52-3.65 (1H, m), 3.90 (2H, t, 7), 3.95 (1H, t, 7), 4.16 (2H, q, 7), 4.15-4.28 (1H, m), 6.74 (2H, d, 8), 7.11 (2H, d, 8), 7.25-7.42 (4H, m), 7.52 (2H, d, 8), 7.78 (2H, d, 8), 7.78 (2H, d, 8). MS 430 (M^+), 384, 299, 193, 179, 165 (100%), 107.

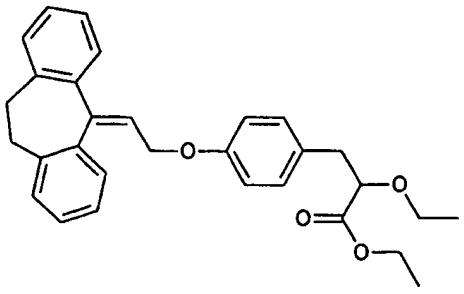
EXAMPLE 6



2-Ethoxy-3-{4-[2-(9*H*-fluoren-9-yl)-ethoxy]-phenyl}-propionic acid

Sodium hydroxide (1M, 2.5 ml, 2.5 mmol) was added to a solution of ethyl 2-ethoxy-3-{4-[2-(9*H*-fluoren-9-yl)-ethoxy]-phenyl}-propionate (0.19 g, 0.44 mmol) in ethanol (5 ml) and the mixture stirred at room temperature for 20h. The resulting mixture was partitioned between water (20 ml) and dichloromethane (20 ml), acidified to pH 1 by adding 1N hydrochloric acid, and the organic phase collected. The aqueous phase was further extracted with dichloromethane (3 x 20 ml) and the combined organics were washed with brine, dried (Na_2SO_4) and evaporated to give the title compound as a waxy solid; 0.17 g (95%).
^{1}H NMR (300MHz, $CDCl_3$) δ: 1.17 (3H, t, 7), 2.46 (2H, q, 7), 2.93 (1H, dd, 16 & 7), 3.04 (1H, dd, 16 &5), 3.38-3.50 (1H, m), 3.50-3.65 (1H, m), 3.90 (2H, t, 7), 4.04 (1H, dd, 7 & 5), 4.23 (1H, t, 7), 6.74 (2H, d, 8), 7.11 (2H, d, 8), 7.25-7.42 (4H, m), 7.52 (2H, d, 8), 7.75 (2H, d, 8).
MS 402 (M^+), 299, 193, 178, 165 (100%), 107.

EXAMPLE 7



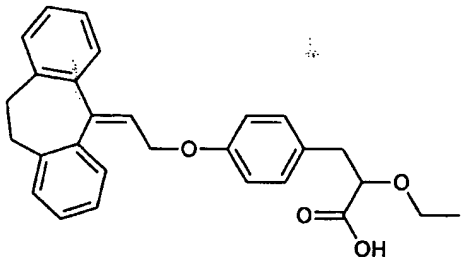
Ethyl 3-{4-[2-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionate

A mixture of ethyl 2-ethoxy-3-(4-hydroxyphenyl)-propionate (2.38 g, 0.01 mol),

5-(2-bromo-1-ethylidene)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (2.75 g, 0.01 mol) and potassium carbonate (5.14 g, 0.03 mol) in dimethylformamide (30 ml) was heated at 100 °C for 20 h. The reaction mixture was diluted with benzene (80 ml), washed with 5% aqueous citric acid (3 x 25 ml) and with saturated $NaHCO_3$ (25 ml), dried ($MgSO_4$) and evaporated. The residue (4.88 g) was purified by column chromatography on silica gel (benzene eluent) to yield the title compound; 2.3 g (53.7%).

Rf 0.32 (SiO_2, benzene/chloroform 4:1). ^1H NMR spectrum (250 MHz, $CDCl_3$) δ: 1.15 (3H, t, 7 Hz), 1.95 (3H, t, 7Hz), 2.92 (2H, d, J=7 Hz), 3.17 (4H, bs), 3.28 (1H, m), 3.58 (1H, m), 3.94 (1H, dd), 4.14 (2H, q, 7Hz), 4.59 (2H, bs), 6.10 (1H, t, 7 Hz), 6.71 (2H, dt), 7.05-7.25 (9H, m), 7.32 (1H, m).

EXAMPLE 8

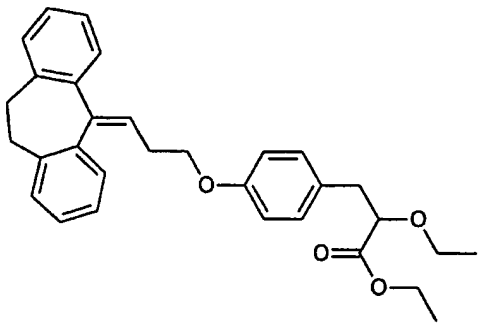


3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionic acid

Ethyl 3-{4-[2-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionate (2.3 g, 53.7 mmol) was dissolved in ethanol (25 ml), 15% sodium hydroxide (7 ml) was added, and the mixture stirred at room temperature for 3 h and stood overnight. The solution was evaporated, water (30 ml) added to the residue, and the mixture acidified to pH 6 with acetic acid (1. 6 ml). The product was extracted with dichloromethane (3 x 20 ml), and the dichloromethane solution washed with water (20 ml), brine (20 ml), dried ($MgSO_4$) and evaporated. The residue was crystallised from a mixture of toluene (8 ml) and n-heptane (8 ml) to give the title compound; 1.60 g (74.4%).

M.p. 147-150 °C. ^1H NMR spectrum (250 MHz, $CDCl_3$) δ: 1.15 (3H, t, 7 Hz), 2.99 (2H, m), 3.17 (4H, bs), 3.42-3.58 (2H, m), 4.01 (1H, dd, 8 and 4 Hz), 4.59 (2H, bd), 6.11 (1H, t, 7 Hz), 6.72 (2H, dt), 7.02-7.35 (10H, m). MA: calculated for $C_{28}H_{28}O_4.1/4H_2O$: C, 77.66%; H, 6.63%; found: C, 77.81%; H, 6.87%.

EXAMPLE 9

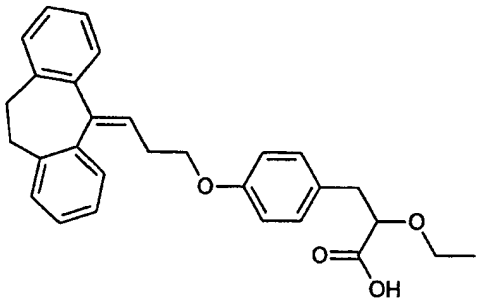


Ethyl 3-(4-(3-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)propoxy)phenyl)-2-ethoxy-propionate

A mixture of 5-(3-mesyloxypropylidene)-10,11-dihydro-dibenzo[*a,d*]cycloheptene (5.0 g, 15.2 mmol), ethyl 3-(4-hydroxyphenyl)-2-ethoxypropionate (3.7 g, 15.5 mmol), potassium carbonate (2.9 g, 21 mmol) and dimethylformamide (10 ml) was heated at 100°C for 5 h. Benzene (200 ml) and water (200 ml) were added and the phases separated. The organic phase was dried, the solvent evaporated, and the product purified by chromatography on silica gel (benzene/chloroform eluent) to give first 2.5 g of 5-propenylidene-10,11-dihydro-5*H*-dibenzo(*a,d*)cycloheptene and then the title compound as an oil; 1.5 g (21%).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.99 (3H, t), 1.27 (3H, t), 2.69 (2H, q), 3.06 (2H, d), 3.17 (4H, bs), 3.45 (1H, m), 3.68 (1H, m), 4.07 (3H, m), 4.27 (2H, q), 6.06 (1H, t), 6.85 (2H, d), 7.10-7.35 (10H, m).

EXAMPLE 10

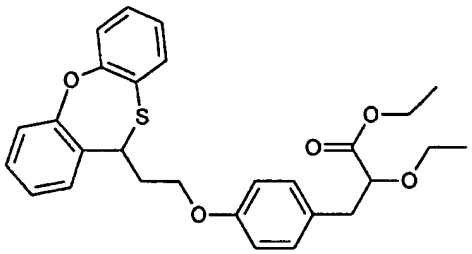


3-(4-(3-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)propoxy)phenyl)-2-ethoxy-propionic acid *L*-Lysine salt.

Ethyl 3-(4-(3-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)propoxy)phenyl)-2-

ethoxy-propionate (1.5 g, 3.2 mmol) was dissolved in ethanol (30 ml) and 20% sodium hydroxide (3 ml) added. After 3 days the ethanol was evaporated, water (50 ml) and hydrochloric acid (2 ml) were added, and the mixture extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and the solvent evaporated. The resulting residue (free acid; 1.1 g, 78 %) was dissolved in ethanol, treated with *L*-lysine monohydrate (0.41 g), and the ethanol evaporated. The residue was triturated with diethyl ether, and the crystalline product collected by filtration, and air dried to give the title salt as the dihydrate; 1.45 g.. M.p. 148-150 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 1.03 (3H, t, 7 Hz), 1.66 (6H, bm), 2.51 (2H, bq), 2.70-2,95 (4H, m), 3.07 (4H, bs), 3.31-3.59 (2H, m), 3.76 (1H, m), 4.02 (2H, t, 6 Hz), 5.91 (1H, t, 7 Hz), 6.26 (8H, bs), 6.75 (2H, bd, 8 Hz), 7.00-7.35 (10H, m). MA: calculated for $C_{29}H_{30}O_4.C_6H_{14}N_2O_2.2H_2O$: C, 67.28%; H, 7.74%; N, 4.48%; found: C, 67.48%; H, 7.87%; N, 4.68%.

EXAMPLE 11

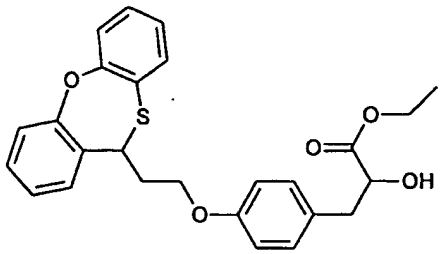


Ethyl 2-ethoxy-3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethoxy]-phenyl}-propionate.

A solution of 2-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethanol (4.1 g, 15.9 mmol) and triethylamine (5 ml) in benzene (80 ml) was treated with methanesulfonyl chloride (2.8 g, 24 mmol) and the mixture stirred for 2 h. The resulting reaction mixture was treated with water (50 ml) and the phases were separated. The organic phase was dried ($MgSO_4$) and the solvent evaporated, affording a residue, which was dissolved in dimethylformamide (10 ml). To this solution were added ethyl 3-(4-hydroxyphenyl)-2-ethoxypropionate (3.8 g, 16 mmol) and potassium carbonate (2.8 g, 20 mmol), and the mixture was heated to 100 °C for 10 h. Water (100 ml) and benzene (150 ml) were added, and the organic phase was collected and washed with water (2 x 50 ml), dried (K_2CO_3) and evaporated. The resulting residue was purified by column chromatography on silica gel (benzene and chloroform as eluents) to give the title compound as an oil: 4.6 g (60 %).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.16 (3H, t), 1.20 (3H, dt, 0.6 and 7 Hz), 2.53-2.80 (2H, m), 2.94 (2H, d, 6.6 Hz), 3.34 (1H, dq, 7.0 and 9.1 Hz), 3.59 (1H, dq, 7 and 9.1 Hz), 3.96 (1H, m), 4.00 (1H, m), 4.15 (2H, q), 4.18 (1H, m), 4.70 (1H, dd, 6.9 and 8.5 Hz), 6.80 (2H, t), 6.93 (1H, ddd, 1.5, 6.8 and 7.8 Hz), 7.01-7.26 (9H, m).

EXAMPLE 12



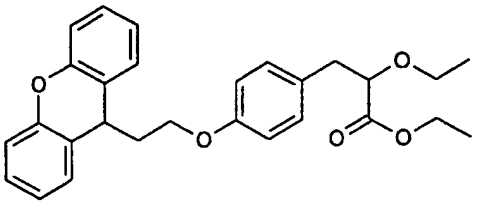
2-Ethoxy-3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yl)-ethoxy]-phenyl}-propionic acid *L*-lysine salt.

Ethyl 2-ethoxy-3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yl)-ethoxy]-phenyl}-propionate (4.6 g, 9.6 mmol) was dissolved in ethanol (90 ml) and 20% sodium hydroxide (9 ml) was added. After 3 days the ethanol was evaporated, water (50 ml) and hydrochloric acid (6 ml) were added, and the mixture was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and the solvent evaporated. The resulting residue (3.8 g, 88%) was dissolved in ethanol, treated with *L*-lysine (1.25 g), the solvent evaporated and the residue triturated with diethyl ether. The resulting crystalline product was collected by filtration and air dried to give the title salt: 4.35 g.

M.p. 153.5-154.5 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 1.00 (3H, bt), 1.2-2.0 (6H, bm), 2.4-3.0 (6H, bm), 3.15 (1H, bm); 3.43 (1H, bm), 3.56 (1H, bm), 3.66 (1H, bs), 4.00 (1H, bs), 4.13 (1H, bs), 4.90 (1H, t, 6.7 Hz), 6.82 (2H, d, 7.9 Hz), 7.00-7.50 (10H, m), 7.82 (5H, bs).

MA: calculated for $C_{26}H_{26}O_5S.C_6H_{14}O_2N_2.1/4H_2O$: C, 63.93%; H, 6.79%; N, 4.66%, S, 5.33%; found: C, 63.90%; H, 7.09%; N, 4.63%; S, 5.41%.

EXAMPLE 13

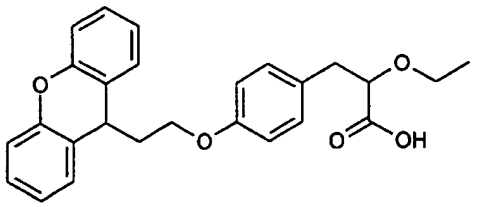


Ethyl 2-ethoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionate

Diethyl azodicarboxylate (40% solution in toluene, 1.61 g, 9.3 mmol) was added dropwise, under argon, over 10 min to a solution of ethyl 3-(4-hydroxyphenyl)-2-ethoxypropionate (2.23 g, 9.3 mmol) and triphenylphosphine (2.43 g, 9.3 mmol) in THF (45 ml). The mixture was stirred for 15 min, then a solution of 2-(9*H*-xanthen-9-yl)ethanol (2.0 g, 9.3 mmol) in THF (10 ml) was added dropwise over 10 min. The resulting mixture was stirred at room temperature for 60 h. The solvent was evaporated, the residue stirred with benzene (20 ml) and the resulting crystalline solid filtered off. The filtrate was evaporated and the residue purified by column chromatography on silica gel (benzene eluent) to give the title compound as an oil: (1.9 g, 45.8 %).

Rf 0.55 (SiO_2, benzene/chloroform 4:1). ^1H NMR (250 MHz, $CDCl_3$) δ: 1.16 (3H, t), 1.21 (3H, t), 2.09 (2H, q) 2.94 (2H, bt), 3.35 (1H, m), 3.60 (1H, m), 3.81 (2H, t), 3.97 (1H, t), 4.15 (2H, q), 4.27 (1H, t), 6.75 (2H, bd), 6.98-7.25 (10H, m), 7.34 (2H, s).

EXAMPLE 14



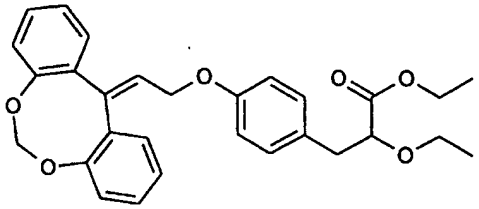
2-Ethoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionic acid

To a solution of ethyl 2-ethoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionate (1.8 g, 4.03 mmol) in ethanol (15 ml) was added a 15% solution of NaOH (4 ml), and the mixture was stirred at room temperature for 5 h, then left to stand overnight. The resulting solution was evaporated, water (50 ml) was added, the mixture was acidified with 15% hydrochloric acid to pH 2, and the products extracted into Et_2O (4 x 30 ml). The combined extracts were

washed with water (30 ml), brine (15 ml), dried ($MgSO_4$) and evaporated to give the title compound as an oil: 1.3 g (77.1 %).

^{1}H NMR spectrum (250 MHz, $CDCl_3$) δ: 1.17 (3H, t, 6.4 Hz), 2.11 (2H, q, 6.4 Hz), 2.80-3.20 (2H, m), 3.40-3.70 (3H, m), 3.82 (2H, t, 6.8 Hz), 4.04 (1H, dd, 4.3 and 7.6 Hz), 4.28 (1H, t, 6.8 Hz), 6.77 (2H, d, 8.6 Hz), 7.01-7.24 (10H, m).

EXAMPLE 15

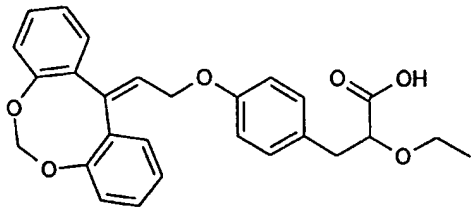


Ethyl 3-(4-(2-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-ethoxypropionate

A mixture of ethyl 3-(4-hydroxyphenyl)-2-ethoxypropionate (0.96 g, 4.0 mmol), 12-(2-bromoethylidene)-12*H*-dibenzo[*d,g*]-1,3-dioxocine (1.07 g, 3.3 mmol) and potassium carbonate (0.45 g, 4.5 mmol) in dimethylformamide (15 ml) was heated to 60 °C for 8.5 h. The reaction mixture was diluted with benzene (50 ml), washed with water (2 x 20 ml), dried ($MgSO_4$) and evaporated. The residue (1.95 g) was purified by column chromatography on silica gel (benzene and benzene/ethyl acetate (9:1) eluents). The benzene fractions were discarded, whilst the benzene/ethyl acetate fractions were evaporated to give the title compound as an oil: 0.97 g (62%).

Rf 0.35 (SiO_2, cyclohexane/ethyl acetate 5:1). ^{1}H NMR spectrum (250 MHz, $CDCl_3$) δ: 1.15 (3H, t, 7 Hz), 1.20 (3H, t, 7.2 Hz), 2.93 (2H, d, 7.1 Hz), 3.33 (1H, m), 3.58 (1H, m), 3.95 (1H, t, 7.2 Hz), 4.14 (2H, q, 7.2 Hz), 4.47 (2H, d, 6.2 Hz), 5.90 (2H, s), 6.21 (1H, t, 6.2 Hz), 6.73 (2H, d, 8.2 Hz), 6.93-7.32 (7H, m), 7.35 (2H, m), 7.38 (1H, m).

EXAMPLE 16



3-(4-(2-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-ethoxypropionic acid *L*-Lysine salt

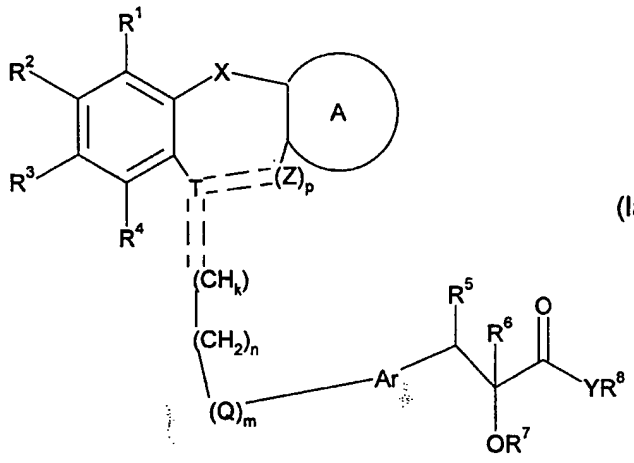
A 15% aqueous solution of NaOH (4 ml) was added to a solution of ethyl 3-(4-(2-(12*H*-dibenzo(*d,g*)-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-ethoxypropionate (0.95 g, 2.0 mmol) in ethanol (15 ml), and the mixture stirred at room temperature for 2 h, then left to stand overnight. The resulting solution was evaporated, water (20 ml) and benzene (25 ml) were added, and the mixture acidified to pH 6 with acetic acid. The benzene layer was separated, and the water layer further extracted with benzene (2 x 10 ml). The combined benzene extracts were washed with water (20 ml), brine (15 ml), dried ($MgSO_4$) and evaporated to give 3-(4-(2-(12*H*-dibenzo(*d,g*)-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-ethoxypropionic acid, : 0.79 g (83.2 %)

This acid (0.76 g, 1.6 mmol) was dissolved in acetone (30 ml), *L*-lysine (0.234 g, 1.6 mmol) and water (3 ml) were added and the mixture stirred at room temperature for 2 h. The solution was filtered, evaporated, and the residue stirred with a mixture of Et_2O (20 ml) and acetone (20 ml) overnight. The resulting solid was collected by filtration, washed with Et_2O (2 x 30 ml) and dried to give the title compound as a partial hydrate: 0.90 g (93.5 %).

M.p. 162-168 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 1.04 (3H, t, 6.8 Hz), 1.38-1.89 (6H, m), 2.75 (3H, m), 2.90 (1H, dd, 14.4 and 4.3 Hz), 3.27 (3H, m), 3.58 (1H, m), 3.75 (1H, m) 4.49 (2H, d, 6.9 Hz), 5.89 (10H, bs), 6.20 (1H, t, 6.3 Hz), 6.75 (2H, d, 7.7 Hz), 6.91-7.52 (10H, m). MA: calculated for $C_{27}H_{26}O_6.C_6H_{14}N_2O_2.1/2H_2O$: C, 65.87%; H, 6.87%; N, 4.66%; found: C, 65.43%; H, 6.98%; N, 4.92%.

Claims:

1. A compound of formula (Ia)



(Ia)

wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-12}alkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, halogen, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

or R^1 and R^2, R^2 and R^3 and/or R^3 and R^4 may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C_{1-6}alkyl;

ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy,

heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-12}alkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, halogen, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

X is a valence bond, -(CHR^9)-, -(CHR^9)-CH_2-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH_2-, -(CHR^9)-CH=CH-, -(CHR^9)-CH_2-CH_2-, -(C=O)-, -O-CH_2-O-, -(NR^9)-, -(NR^9)-S(O_2)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH_2-(SO)-, -S-, -(SO)-, -(SO_2)-, -CH_2-(SO_2)-, -CH_2-O-CH_2-, wherein R^9 is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C_{1-12}alkyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{13}, or -SO_2R^{14}, wherein R^{13} and R^{14} independently of each other are selected from hydroxy, halogen, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl;

T is >N-, >CH-, >C<, -CH_2-N<;

Z is -CH_2-, =CH-, >N-, -O-, -S-, >CO, >SO, >SO_2, >NR^{11}, wherein R^{11} is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C_{1-12}alkyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{15}, or -SO_2R^{16}, wherein R^{15} and R^{16} independently of each other are selected from hydroxy, halogen, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl;

Q is -O-, -S-, $>SO_2$, $>NR^{12}$, wherein R^{12} is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C_{1-12}alkyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C_{1-12}alkylamino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{17}, or -SO_2R^{18}, wherein R^{17} and R^{18} independently of each other are selected from hydroxy, halogen, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl;

k is 1 or 2;

T==$(Z)_p$ and T==$(CH)_k$ independently of each other represents a single bond or a double bond, provided that both are not a double bond at the same time;

Ar represents arylene, heteroarylene, or a divalent heterocyclic group optionally substituted with one or more C_{1-6}alkyl or aryl;

R^5 represents hydrogen, hydroxy, halogen, C_{1-12}alkoxy, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R^5 forms a bond together with R^6;

R^6 represents hydrogen, hydroxy, halogen, C_{1-12}alkoxy, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, acyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R^6 forms a bond together with R^5;

R^7 represents hydrogen, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, aryl, aralkyl, C_{1-12}alkoxyC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, C_{1-12}alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

R^8 represents hydrogen, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

Y represents oxygen, sulphur or NR^{10}, where R^{10} represents hydrogen, C_{1-12}alkyl, aryl, hydroxyC_{1-12}alkyl or aralkyl groups or when Y is NR^{10}, R^8 and R^{10} may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C_{1-6}alkyl;

n is an integer ranging from 0 to 3;

m is an integer ranging from 0 to 1;

p is an integer ranging from 0 to 1;

with the proviso that T is not N when p is 0;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, or cyano;
or R^1 and R^2, R^2 and R^3 and/or R^3 and R^4 may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C_{1-6}alkyl.

3. A compound according to anyone of the preceding claims wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino.

4. A compound according to anyone of the preceding claims wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, or C_{1-7}alkylthio.

5. A compound according to anyone of the preceding claims wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, C_{1-7}alkyl, C_{1-7}alkoxy, aryl, or aryloxy.

6. A compound according to anyone of the preceding claims wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, or C_{1-7}alkoxy.

7. A compound according to anyone of the preceding claims wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, perhalomethyl, or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, or cyano;

8. A compound according to anyone of the preceding claims wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl.

9. A compound according to anyone of the preceding claims wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, hydroxy, cyano, or C_{1-7}alkyl, C_{1-7}alkoxy.

10. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(CHR^9)-CH=CH-, -(CHR^9)-CH$_2$-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-, -(NR^9)-S(O$_2$)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)-, -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen, halogen, hydroxy, cyano, C$_{1-7}$alkyl, C$_{1-7}$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C$_{1-7}$alkyl-amino, arylamino, aralkylamino, aminoC$_{1-7}$alkyl, C$_{1-7}$alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C$_{1-7}$alkoxyC$_{1-7}$alkyl, aryloxyC$_{1-7}$alkyl, aralkoxyC$_{1-7}$alkyl, C$_{1-7}$alkylthio, thioC$_{1-7}$alkyl, C$_{1-7}$alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{13}, or -SO$_2$R^{14}, wherein R^{13} and R^{14} independently of each other are selected from hydroxy, C$_{1-6}$alkoxy, amino optionally substituted with one or more C$_{1-6}$alkyl, perhalomethyl or aryl.

11. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(CHR^9)-CH=CH-, -(CHR^9)-CH$_2$-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-, -(NR^9)-S(O$_2$)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)-, -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen, halogen, hydroxy, C$_{1-7}$alkyl, C$_{1-7}$alkoxy, aryl.

12. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)-, -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen, halogen, hydroxy, C$_{1-7}$alkyl, C$_{1-7}$alkoxy, aryl.

13. A compound according to anyone of the preceding claims wherein T is >N-, >CH- or >C<.

14. A compound according to anyone of the preceding claims wherein Z is -CH$_2$-, =CH-, >N-, -O-, -S-, >CO, >SO, >SO$_2$, >NR^{11}, wherein R^{11} is hydrogen, C$_{1-7}$alkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, aminoC$_{1-7}$alkyl, C$_{1-7}$alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C$_{1-7}$alkoxyC$_{1-7}$alkyl, aryloxyC$_{1-7}$alkyl, aralkoxyC$_{1-7}$alkyl, thioC$_{1-7}$alkyl, -COR^{15}, or -SO$_2$R^{16}, wherein

R^{15} and R^{16} independently of each other are selected from hydroxy, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl.

15. A compound according to anyone of the preceding claims wherein Z is $-CH_2-$, $=CH-$, $>N-$, $-O-$, $-S-$, $>CO$, $>SO$, $>SO_2$, $>NR^{11}$, wherein R^{11} is hydrogen, C_{1-7}alkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl.

16. A compound according to anyone of the preceding claims wherein Z is $-CH_2-$, $=CH-$, $>N-$, $-O-$, $-S-$, $>CO$, $>SO$, $>SO_2$, $>NR^{11}$, wherein R^{11} is hydrogen, C_{1-7}alkyl.

17. A compound according to anyone of the preceding claims wherein Q is $-O-$, $-S-$ or $>NR^{12}$, wherein R^{12} is hydrogen, or methyl.

18. A compound according to anyone of the preceding claims wherein Ar represents arylene optionally substituted with one or more C_{1-6}alkyl or aryl.

19. A compound according to anyone of the preceding claims wherein Ar represents phenyl.

20. A compound according to anyone of the preceding claims wherein R^5 represents hydrogen, hydroxy, halogen, C_{1-7}alkoxy, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl or aralkyl, or R^5 forms a bond together with R^6.

21. A compound according to anyone of the preceding claims wherein R^5 represents hydrogen or R^5 forms a bond together with R^6.

22. A compound according to anyone of the preceding claims wherein R^6 represents hydrogen, C_{1-7}alkoxy, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, acyl or aralkyl, or R^6 forms a bond together with R^5.

23. A compound according to anyone of the preceding claims wherein R^6 represents hydrogen or R^6 forms a bond together with R^5.

24. A compound according to anyone of the preceding claims wherein R^7 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl, aralkyl, C_{1-7}alkoxyC_{1-7}alkyl, C_{1-7}alkoxycarbonyl, aryloxycarbonyl, C_{1-7}alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups.

25. A compound according to anyone of the preceding claims wherein R^7 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl or C_{2-7}-alkynyl.

26. A compound according to anyone of the preceding claims wherein R^7 represents C_{1-2}alkyl.

27. A compound according to anyone of the preceding claims wherein R^8 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

28. A compound according to anyone of the preceding claims wherein R^8 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl or aralkyl.

29. A compound according to anyone of the preceding claims wherein R^8 represents hydrogen or C_{1-2}alkyl.

30. A compound according to anyone of the preceding claims wherein Y represents oxygen, sulphur or NR^{10}, where R^{10} represents hydrogen, C_{1-7}alkyl, aryl, hydroxyC_{1-7}alkyl or aralkyl groups.

31. A compound according to anyone of the preceding claims wherein Y represents oxygen.

32. A compound according to anyone of the preceding claims wherein A is benzo.

33. A compound according to anyone of the preceding claims wherein X is -O-.

34. A compound according to anyone of the preceding claims wherein X is -S-.

35. A compound according to anyone of the preceding claims wherein X is -(CHR^9)-CH$_2$-, wherein R^9 is H.

36. A compound according to anyone of the preceding claims wherein X is -O-(CHR^9)-, wherein R^9 is H.

37. A compound according to anyone of the preceding claims wherein X is -S-(CHR^9)-, wherein R^9 is H.

38. A compound according to anyone of the preceding claims wherein X is -(NR^9)-CH$_2$, wherein R^9 is C$_{1-12}$-alkyl, preferably methyl.

39. A compound according to anyone of the preceding claims X is -O-(CHR^9)-, wherein R^9 is H.

40. A compound according to anyone of the preceding claims wherein X is -(C=O)-.

41. A compound according to anyone of the preceding claims wherein X is -(CHR^9)-, wherein R^9 is H.

42. A compound according to anyone of the preceding claims wherein X is -O-.

43. A compound according to anyone of the preceding claims wherein X is -(CHR^9)-CH$_2$-CH$_2$-, wherein R^9 is H.

44. A compound according to anyone of the preceding claims wherein X is a valence bond.

45. A compound according to anyone of the preceding claims wherein R^1, R^2, R^3 and R^4 are H.

46. A compound according to anyone of the preceding claims wherein n is 1.

47. A compound according to anyone of the preceding claims wherein n is 2.

48. A compound according to anyone of the preceding claims wherein m is 1.

49. A compound according to anyone of the preceding claims wherein k is 0.

50. A compound according to anyone of the preceding claims wherein k is 1.

51. A compound according to anyone of the preceding claims wherein Q is -O-.

52. A compound according to anyone of the preceding claims wherein T==$(CH)_k$ represents a single bond or a double bond.

53. A compound according to anyone of the preceding claims wherein T is >CH- or >C<.

54. A compound according to anyone of the preceding claims wherein T is >N- and p is 1.

55. A compound according to anyone of the preceding claims wherein Z is -CH_2- or >CO and p is 1.

56. A compound according to anyone of the preceding claims wherein R^5 is H.

57. A compound according to anyone of the preceding claims wherein R^6 is H.

58. A compound according to anyone of the preceding claims wherein R^7 is ethyl.

59. A compound according to anyone of the preceding claims wherein R^8 is H.

60. A compound according to anyone of the preceding claims wherein R^8 is ethyl.

62. A compound according to anyone of the preceding claims wherein Z is -S- and T is >CH-.

63. A compound according to anyone of the preceding claims wherein Z is -O- and T is >CH-.

64. A compound according to anyone of the preceding claims wherein Ar is phenylene.

65. A compound according to anyone of the preceding claims wherein p is 0.

66. The compound according to claim 1 which is:

2-Ethoxy-3-[4-(2-xanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,

2-Methoxy-3-[4-(2-xanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-xanthen-9-ylidene-propoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-thioxanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,

2-Methoxy-3-[4-(2-thioxanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-thioxanthen-9-ylidene-propoxy)-phenyl]-propionic acid,

2-Ethoxy-3-{4-[2-(9*H*-thioxanthen-9-yl)-ethoxy]-phenyl}-propionic acid,

3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(6*H*-Dibenzo[*b,e*]oxepin-11-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

2-Ethoxy-3-{4-[2-(11*H*-10-thia-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionic acid,

3-{4-[2-(5,11-Dihydro-10-thia-dibenzo[*a,d*]cyclohepten-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

2-Ethoxy-3-{4-[2-(5-methyl-5,6-dihydro-dibenzo[*b,e*]azepin-11-ylidene)-ethoxy]-phenyl}-propionic acid,

2-Ethoxy-3-{4-[2-(11-oxo-6,11-dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-propionic acid,

3-{4-[2-(6,11-Dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(6,11-Dioxo-6,11-dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(11*H*-Dibenzo[*b,f*][1,4]oxazepin-10-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(11,12-Dihydro-dibenzo[*a,e*]cycloocten-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

Ethyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,

Propyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,

Butyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,

Pentyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,
Hexyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,
Heptyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,
N,N-Dimethyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,
N-Methyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,
N,N-Diethyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,
N-Ethyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,
N-Benzyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,
N-Propyl 2-ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionamide,
Ethyl 3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-2-methoxy-propionate,
Ethyl 3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-2-propoxy-propionate,
Ethyl 2-butoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-2-pentyloxy-propionate,
Ethyl 3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-2-hexyloxy-propionate,
Ethyl 3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-2-heptyloxy-propionate,
Ethyl 3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-2-methoxy-propionate,
Ethyl 2-ethoxy-3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-propionate,
Ethyl 3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-2-propoxy-propionate,
Ethyl 2-butoxy-3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-propionate,
Ethyl 3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-2-pentyloxy-propionate,
Ethyl 3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-2-hexyloxy-propionate,
Ethyl 3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-2-heptyloxy-propionate,
Ethyl 3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-2-methoxy-propionate,
Ethyl 2-ethoxy-3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-propionate,
Ethyl 3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-2-propoxy-propionate,
Ethyl 2-butoxy-3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-propionate,
Ethyl 3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-2-pentyloxy-propionate,
Ethyl 3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-2-hexyloxy-propionate,
Ethyl 3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-2-heptyloxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{2-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{2-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{2-butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{2-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{2-butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,

Ethyl 2-ethoxy-3-[4-(2-{3-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{3-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{3-butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{3-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{3-butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{4-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{4-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{4-butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{4-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-{4-butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionate,
Ethyl 2-ethoxy-3-[4-(2-{3,6-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{2,7-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{4,5-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{3,6-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{2,7-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
Ethyl 2-ethoxy-3-[4-(2-{4,5-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionate,
3-[4-(2-Fluoren-9-ylidene-ethoxy)-phenyl]-2-methoxy-propionic acid,
2-Ethoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionic acid,
3-[4-(2-Fluoren-9-ylidene-ethoxy)-phenyl]-2-propoxy-propionic acid,
2-Butoxy-3-[4-(2-fluoren-9-ylidene-ethoxy)-phenyl]-propionic acid,
3-[4-(2-Fluoren-9-ylidene-ethoxy)-phenyl]-2-pentyloxy-propionic acid,
3-[4-(2-Fluoren-9-ylidene-ethoxy)-phenyl]-2-hexyloxy-propionic acid,
3-[4-(2-Fluoren-9-ylidene-ethoxy)-phenyl]-2-heptyloxy-propionic acid,
3-[4-(3-Fluoren-9-ylidene-propoxy)-phenyl]-2-methoxy-propionic acid,
2-Ethoxy-3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-propionic acid,
3-[4-(3-Fluoren-9-ylidene-propoxy)-phenyl]-2-propoxy-propionic acid,
2-Butoxy-3-[4-(3-fluoren-9-ylidene-propoxy)-phenyl]-propionic acid,
3-[4-(3-Fluoren-9-ylidene-propoxy)-phenyl]-2-pentyloxy-propionic acid,
3-[4-(3-Fluoren-9-ylidene-propoxy)-phenyl]-2-hexyloxy-propionic acid,
3-[4-(3-Fluoren-9-ylidene-propoxy)-phenyl]-2-heptyloxy-propionic acid,
3-[4-(4-Fluoren-9-ylidene-butoxy)-phenyl]-2-methoxy-propionic acid,
2-Ethoxy-3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-propionic acid,
3-[4-(4-Fluoren-9-ylidene-butoxy)-phenyl]-2-propoxy-propionic acid,
2-Butoxy-3-[4-(4-fluoren-9-ylidene-butoxy)-phenyl]-propionic acid,

3-[4-(4-Fluoren-9-ylidene-butoxy)-phenyl]-2-pentyloxy-propionic acid,

3-[4-(4-Fluoren-9-ylidene-butoxy)-phenyl]-2-hexyloxy-propionic acid,

3-[4-(4-Fluoren-9-ylidene-butoxy)-phenyl]-2-heptyloxy-propionic acid,

2-Ethoxy-3-[4-(2-{2-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-{2-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

3-[4-(2-{2-Butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-{2-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

3-[4-(2-{2-Butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-{3-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-{3-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

3-[4-(2-{3-Butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-{3-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

3-[4-(2-{3-Butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-{4-methoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-{4-propoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

3-[4-(2-{4-Butoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-{4-methyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

3-[4-(2-{4-Butyl-fluoren-9-ylidene}-ethoxy)-phenyl]-2-ethoxy-propionic acid,

2-Ethoxy-3-[4-(2-{3,6-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-{2,7-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-{4,5-Dimethoxy-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-{3,6-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-{2,7-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

2-Ethoxy-3-[4-(2-{4,5-Dimethyl-fluoren-9-ylidene}-ethoxy)-phenyl]-propionic acid,

Ethyl 3-{4-[2-(6*H*-dibenzo[*b,e*]oxepin-11-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionate,

Ethyl 3-{4-[3-(6*H*-dibenzo[*b,e*]oxepin-11-ylidene)-propoxy]-phenyl}-2-ethoxy-propionate,

Ethyl 3-{4-[4-(6*H*-dibenzo[*b,e*]oxepin-11-ylidene)-butoxy]-phenyl}-2-ethoxy-propionate,

3-{4-[3-(6*H*-Dibenzo[*b,e*]oxepin-11-ylidene)-propoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[4-(6*H*-Dibenzo[*b,e*]oxepin-11-ylidene)-butoxy]-phenyl}-2-ethoxy-propionic acid,

Ethyl 3-{4-[2-(6*H*-dibenzo[*b,e*]oxepin-11-ylidene)-ethoxy]-phenyl}-2-methoxy-propionate,

Ethyl 3-{4-[3-(6*H*-dibenzo[*b,e*]oxepin-11-ylidene)-propoxy]-phenyl}-2-methoxy-propionate,

Ethyl 3-{4-[4-(6*H*-dibenzo[*b,e*]oxepin-11-ylidene)-butoxy]-phenyl}-2-methoxy-propionate,

3-{4-[2-(6*H*-Dibenzo[*b,e*]oxepin-11-ylidene)-ethoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[3-(6*H*-Dibenzo[*b,e*]oxepin-11-ylidene)-propoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[4-(6*H*-Dibenzo[*b*,*e*]oxepin-11-ylidene)-butoxy]-phenyl}-2-methoxy-propionic acid,
Ethyl 3-{4-[2-(6*H*-dibenzo[*b*,*e*]oxepin-11-ylidene)-ethoxy]-phenyl}-2-propoxy-propionate,
Ethyl 3-{4-[3-(6*H*-dibenzo[*b*,*e*]oxepin-11-ylidene)-propoxy]-phenyl}-2-propoxy-propionate,
Ethyl 3-{4-[4-(6*H*-dibenzo[*b*,*e*]oxepin-11-ylidene)-butoxy]-phenyl}-2-propoxy-propionate,
3-{4-[2-(6*H*-Dibenzo[*b*,*e*]oxepin-11-ylidene)-ethoxy]-phenyl}-2-propoxy-propionic acid,
3-{4-[3-(6*H*-Dibenzo[*b*,*e*]oxepin-11-ylidene)-propoxy]-phenyl}-2-propoxy-propionic acid,
3-{4-[4-(6*H*-Dibenzo[*b*,*e*]oxepin-11-ylidene)-butoxy]-phenyl}-2-propoxy-propionic acid,
Ethyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,
Propyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,
Butyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,
Pentyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,
Hexyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,
Heptyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,
N,*N*-Dimethyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,
N-Methyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,
N,*N*-Diethyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,
N-Ethyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,
N-Benzyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,
N-Propyl 2-ethoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionamide,
Ethyl 3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-2-methoxy-propionate,
Ethyl 3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-2-propoxy-propionate,
Ethyl 2-butoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionate,
Ethyl 3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-2-pentyloxy-propionate,
Ethyl 3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-2-hexyloxy-propionate,
Ethyl 3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-2-heptyloxy-propionate,
Ethyl 3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-2-methoxy-propionate,
Ethyl 2-ethoxy-3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-propionate,
Ethyl 3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-2-propoxy-propionate,
Ethyl 2-butoxy-3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-propionate,
Ethyl 3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-2-pentyloxy-propionate,
Ethyl 3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-2-hexyloxy-propionate,
Ethyl 3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-2-heptyloxy-propionate,
Ethyl 3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-2-methoxy-propionate,
Ethyl 2-ethoxy-3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-propionate,

Ethyl 3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-2-propoxy-propionate,

Ethyl 2-butoxy-3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-propionate,

Ethyl 3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-2-pentyloxy-propionate,

Ethyl 3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-2-hexyloxy-propionate,

Ethyl 3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-2-heptyloxy-propionate,

Ethyl 2-ethoxy-3-[4-(2-{9*H*-2-methoxyfluoren-9-yl)}-ethoxy)-phenyl]-propionate,

Ethyl 2-ethoxy-3-[4-(2-{9*H*-2-propoxyfluoren-9-yl)}-ethoxy)-phenyl]-propionate,

Ethyl 3-[4-(2-(9*H*-2-butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-2-methylfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 3-[4-(2-(9*H*-2-butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-3-methoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-3-propoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 3-[4-(2-(9*H*-3-butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-3-methylfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 3-[4-(2-(9*H*-3-butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-4-methoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-4-propoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 3-[4-(2-(9*H*-4-butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-4-methylfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 3-[4-(2-(9*H*-4-butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-3,6-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-2,7-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-4,5-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-3,6-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-2,7-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionate,

Ethyl 2-ethoxy-3-[4-(2-(9*H*-4,5-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionate,

3-[4-(2-(9*H*-Fluoren-9-yl)-ethoxy)-phenyl]-2-methoxy-propionic acid,

2-Ethoxy-3-[4-(2-(9H-fluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

3-[4-(2-(9*H*-Fluoren-9-yl)-ethoxy)-phenyl]-2-propoxy-propionic acid,

2-Butoxy-3-[4-(2-(9*H*-fluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

3-[4-(2-(9*H*-Fluoren-9-yl)-ethoxy)-phenyl]-2-pentyloxy-propionic acid,

3-[4-(2-(9*H*-Fluoren-9-yl)-ethoxy)-phenyl]-2-hexyloxy-propionic acid,

3-[4-(2-(9*H*-Fluoren-9-yl)-ethoxy)-phenyl]-2-heptyloxy-propionic acid,

3-[4-(3-(9*H*-Fluoren-9-yl)-propoxy)-phenyl]-2-methoxy-propionic acid,

2-Ethoxy-3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-propionic acid,
3-[4-(3-(9*H*-Fluoren-9-yl)-propoxy)-phenyl]-2-propoxy-propionic acid,
2-Butoxy-3-[4-(3-(9*H*-fluoren-9-yl)-propoxy)-phenyl]-propionic acid,
3-[4-(3-(9*H*-Fluoren-9-yl)-propoxy)-phenyl]-2-pentyloxy-propionic acid,
3-[4-(3-(9*H*-Fluoren-9-yl)-propoxy)-phenyl]-2-hexyloxy-propionic acid,
3-[4-(3-(9*H*-Fluoren-9-yl)-propoxy)-phenyl]-2-heptyloxy-propionic acid,
3-[4-(4-(9*H*-Fluoren-9-yl)-butoxy)-phenyl]-2-methoxy-propionic acid,
2-Ethoxy-3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-propionic acid,
3-[4-(4-(9*H*-Fluoren-9-yl)-butoxy)-phenyl]-2-propoxy-propionic acid,
2-Butoxy-3-[4-(4-(9*H*-fluoren-9-yl)-butoxy)-phenyl]-propionic acid,
3-[4-(4-(9*H*-Fluoren-9-yl)-butoxy)-phenyl]-2-pentyloxy-propionic acid,
3-[4-(4-(9*H*-Fluoren-9-yl)-butoxy)-phenyl]-2-hexyloxy-propionic acid,
3-[4-(4-(9*H*-Fluoren-9-yl)-butoxy)-phenyl]-2-heptyloxy-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-2-methoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-2-propoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
3-[4-(2-(9*H*-2-Butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-2-methylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
3-[4-(2-(9*H*-2-Butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-3-methoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-3-propoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
3-[4-(2-(9*H*-3-Butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-3-methylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
3-[4-(2-(9*H*-3-Butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-4-methoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-4-propoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
3-[4-(2-(9*H*-4-Butoxyfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-4-methylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
3-[4-(2-(9*H*-4-Butylfluoren-9-yl)-ethoxy)-phenyl]-2-ethoxy-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-3,6-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-2,7-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-4,5-dimethoxyfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-3,6-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-2,7-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-(9*H*-4,5-dimethylfluoren-9-yl)-ethoxy)-phenyl]-propionic acid,

Ethyl 3-{4-[2-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionate,

Ethyl 3-{4-[3-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-ethoxy-propionate,

Ethyl 3-{4-[4-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-ethoxy-propionate,

3-{4-[3-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[4-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-ethoxy-propionic acid,

Ethyl 3-{4-[2-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-methoxy-propionate,

Ethyl 3-{4-[3-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-methoxy-propionate,

Ethyl 3-{4-[4-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-methoxy-propionate,

3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[3-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[4-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-methoxy-propionic acid,

Ethyl 3-{4-[2-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-propoxy-propionate,

Ethyl 3-{4-[3-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-propoxy-propionate,

Ethyl 3-{4-[4-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-propoxy-propionate,

3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-propoxy-propionic acid,

3-{4-[3-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-propoxy-propionic acid,

3-{4-[4-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-butoxy]-phenyl}-2-propoxy-propionic acid,

Ethyl 3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethoxy]-phenyl}-2-ethoxy-propionate,

Ethyl 3-{4-[3-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-propoxy]-phenyl}-2-ethoxy-propionate,

Ethyl 3-{4-[4-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-butoxy]-phenyl}-2-ethoxy-propionate,

3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[3-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[4-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-butoxy]-phenyl}-2-ethoxy-propionic acid,

Ethyl 3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethoxy]-phenyl}-2-methoxy-propionate,

Ethyl 3-{4-[3-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-propoxy]-phenyl}-2-methoxy-propionate,

Ethyl 3-{4-[4-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-butoxy]-phenyl}-2-methoxy-propionate,

3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[3-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-propoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[4-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-butoxy]-phenyl}-2-methoxy-propionic acid,

Ethyl 3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethoxy]-phenyl}-2-propoxy-propionate,

Ethyl 3-{4-[3-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-propoxy]-phenyl}-2-propoxy-propionate,

Ethyl 3-{4-[4-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-butoxy]-phenyl}-2-propoxy-propionate,

3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-ethoxy]-phenyl}-2-propoxy-propionic acid,

3-{4-[3-(11*H*-5-oxa-10-thia-dibenzo[*a*,*d*]cyclohepten-11-yl)-propoxy]-phenyl}-2-propoxy-propionic acid,

3-{4-[4-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yl)-butoxy]-phenyl}-2-propoxy-propionic acid,

Ethyl 2-methoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionate,

2-Methoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionic acid,

Ethyl 2-ethoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionate,

2-Ethoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionic acid,

Ethyl 2-propoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionate,

2-Propoxy-3-{4-[2-(9*H*-xanthen-9-yl)ethoxy]phenyl}propionic acid,

Ethyl 2-methoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionate,

2-Methoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionic acid,

Ethyl 2-ethoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionate,

2-Ethoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionic acid,

Ethyl 2-propoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionate,

2-Propoxy-3-{4-[3-(9*H*-xanthen-9-yl)propoxy]phenyl}propionic acid,

Ethyl 2-methoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionate,

2-Methoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionic acid,

Ethyl 2-ethoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionate,

2-Ethoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionic acid,

Ethyl 2-propoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionate,

2-Propoxy-3-{4-[4-(9*H*-xanthen-9-yl)butoxy]phenyl}propionic acid,

Ethyl 3-(4-(2-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-methoxy-propionate,

3-(4-(2-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-methoxypropionic acid,

Ethyl 3-(4-(3-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-methoxy-propionate,

3-(4-(3-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-methoxypropionic acid,

Ethyl 3-(4-(4-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-methoxy-propionate,

3-(4-(4-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-methoxypropionic acid,

Ethyl 3-(4-(2-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-ethoxypropionate,

3-(4-(2-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-ethoxypropionic acid,

Ethyl 3-(4-(3-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-ethoxy-propionate,

3-(4-(3-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-ethoxypropionic acid,
Ethyl 3-(4-(4-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-ethoxypropionate,
3-(4-(4-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-ethoxypropionic acid,
Ethyl 3-(4-(2-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-propoxy-propionate,
3-(4-(2-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)ethoxy)phenyl)-2-propoxypropionic acid,
Ethyl 3-(4-(3-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-propoxy-propionate,
3-(4-(3-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)propoxy)phenyl)-2-propoxypropionic acid,
Ethyl 3-(4-(4-(12*H*-dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-propoxy-propionate,
3-(4-(4-(12*H*-Dibenzo[*d,g*]-1,3-dioxocine-12-ylidene)butoxy)phenyl)-2-propoxypropionic acid,
Ethyl 2-ethoxy-3-[4-(2-{indeno[2,1-*b*]pyridin-9-ylidene}-ethoxy)-phenyl]-propionate,
2-Ethoxy-3-[4-(2-{indeno[2,1-*b*]pyridin-9-ylidene}-ethoxy)-phenyl]-propionic acid,
Ethyl 2-ethoxy-3-{4-[2-(9*H*-indeno[2,1-*b*]pyridin-9-yl)-ethoxy]-phenyl}-propionate,
2-Ethoxy-3-{4-[2-(9*H*-indeno[2,1-*b*]pyridin-9-yl)-ethoxy]-phenyl}-propionic acid,
Ethyl 2-ethoxy-3-{4-[2-(1-oxa-cyclopenta[*a*]inden-8-ylidene)-ethoxy]-phenyl}-propionate,
2-Ethoxy-3-{4-[2-(1-oxa-cyclopenta[*a*]inden-8-ylidene)-ethoxy]-phenyl}-propionic acid,
Ethyl 2-ethoxy-3-{4-[2-(8*H*-1-oxa-cyclopenta[*a*]inden-8-yl)-ethoxy]-phenyl}-propionate,
2-Ethoxy-3-{4-[2-(8*H*-1-oxa-cyclopenta[*a*]inden-8-yl)-ethoxy]-phenyl}-propionic acid,
Ethyl 2-ethoxy-3-{4-[2-(dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionate,
2-Ethoxy-3-{4-[2-(dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionic acid,
Ethyl 2-ethoxy-3-{4-[2-(10-methyldibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionate,
2-Ethoxy-3-{4-[2-(10-methyldibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionic acid,
Ethyl 2-ethoxy-3-{4-[2-(10-oxo-10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionate,
2-Ethoxy-3-{4-[2-(10-oxo-10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionic acid,
Ethyl 2-ethoxy-3-{4-[2-(10-methyl-10*H*-acridin-9-ylidene)-ethoxy]-phenyl}-propionate,
2-Ethoxy-3-{4-[2-(10-methyl-10*H*-acridin-9-ylidene)-ethoxy]-phenyl}-propionic acid,
Ethyl 3-{4-[2-(10*H*-acridin-9-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionate,

3-{4-[2-(10*H*-Acridin-9-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
Ethyl 2-ethoxy-3-{4-[2-(10-oxo-10*H*-anthracen-9-ylidene)-ethoxy]-phenyl}-propionate,
2-Ethoxy-3-{4-[2-(10-oxo-10*H*-anthracen-9-ylidene)-ethoxy]-phenyl}-propionic acid,
Ethyl 2-ethoxy-3-{4-[2-(9*H*-thioxanthen-9-yl)-ethoxy]-phenyl}-propionate,
Ethyl 2-ethoxy-3-{4-[2-(11*H*-10-thia-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionate;
or a pharmaceutically acceptable salt thereof.

67. The compound according to claim 1 which is:
2-Ethoxy-3-[4-(2-xanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,
2-Methoxy-3-[4-(2-xanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-xanthen-9-ylidene-propoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-thioxanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,
2-Methoxy-3-[4-(2-thioxanthen-9-ylidene-ethoxy)-phenyl]-propionic acid,
2-Ethoxy-3-[4-(2-thioxanthen-9-ylidene-propoxy)-phenyl]-propionic acid,
2-Ethoxy-3-{4-[2-(9*H*-thioxanthen-9-yl)-ethoxy]-phenyl}-propionic acid,
3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[2-(10,11-Dihydro-dibenzo[*a,d*]cyclohepten-5-ylidene)-propoxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[2-(6*H*-Dibenzo[*b,e*]oxepin-11-ylidene)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
2-Ethoxy-3-{4-[2-(11*H*-10-thia-dibenzo[*a,d*]cyclohepten-5-ylidene)-ethoxy]-phenyl}-propionic acid,
3-{4-[2-(5,11-Dihydro-10-thia-dibenzo[*a,d*]cyclohepten-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
2-Ethoxy-3-{4-[2-(5-methyl-5,6-dihydro-dibenzo[*b,e*]azepin-11-ylidene)-ethoxy]-phenyl}-propionic acid,
2-Ethoxy-3-{4-[2-(11-oxo-6,11-dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-propionic acid,
3-{4-[2-(6,11-Dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[2-(6,11-Dioxo-6,11-dihydro-dibenzo[*b,e*]azepin-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[2-(11*H*-Dibenzo[*b,f*][1,4]oxazepin-10-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(11,12-Dihydro-dibenzo[*a,e*]cycloocten-5-yl)-ethoxy]-phenyl}-2-ethoxy-propionic acid; or a pharmaceutically acceptable salt thereof.

68. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

69. A composition according to claim 68 in unit dosage form, comprising from about 0.05 to about 100 mg, preferably from about 0.1 to about 50 mg of the compound according to any-one of the preceding compound claims or a pharmaceutically acceptable salt thereof.

70. A pharmaceutical composition useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the composition comprising, as an active ingredient, a compound according to any-one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

71. A pharmaceutical composition useful in the treatment and/or prevention of diabetes and/or obesity, the composition comprising, as an active ingredient, a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

72. A pharmaceutical composition for diabetes and/or obesity, the composition comprising, as an active ingredient, a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

73. A pharmaceutical composition according to any one of the claims 68-72 for oral, nasal, transdermal, pulmonal, or parenteral administration.

74. A method for the treatment of ailments, the method comprising administering to a subject in need thereof an effective amount of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding composition claims.

75. A method for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to anyone of the preceding claims 34-39.

76. A method for the treatment and/or prevention of diabetes and/or obesity, the method comprising administering to a subject in need thereof an effective amount of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to anyone of the preceding claims 68-73.

77. The method according to claims 74-76, wherein the effective amount of the compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt or ester thereof is in the range of from about 0.05 to about 100 mg per day, preferably from about 0.1 to about 50 mg per day.

78. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament.

79. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

80. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of diabetes and/or obesity.

81. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of diabetes and obesity.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00569

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 69/734, C07C 59/72, C07D 311/82, C07D 327/02, C07D 313/12, C07D 321/12, A61K 31/335, A61K 31/185, 31/215, A61K 31/39, A61P 3/10, 3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9919313 A1 (DR. REDDY'S RESEARCH FOUNDATION), 22 April 1999 (22.04.99) --	1-81
X	STN International, File CAPLUS, CAPLUS accession no. 1998:430714, Document no. 129:108904, Fukazawa, Nobuyuki et al: "Preparation of hydroxybenzoic acids, their use as cell adhesion inhibitors, and their pharmaceutical compositions", JP,A2,10182550, 19980707 --	1-81
X	WO 9604260 A1 (SMITHKLINE BEECHAM PLC), 15 February 1996 (15.02.96) --	1-81

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2000	16 -02- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/Els Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00569

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9604261 A1 (SMITHKLINE BEECHAM PLC), 15 February 1996 (15.02.96)	1-81
	--	
X	WO 9725042 A1 (SMITHKLINE BEECHAM P.L.C.), 17 July 1997 (17.07.97)	1-81
	--	
A	WO 9736579 A1 (GLAXO GROUP LIMITED), 9 October 1997 (09.10.97)	1-81
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00569

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 74-77
because they relate to subject matter not required to be searched by this Authority, namely:

see next page

2. ☒ Claims Nos.: 1-81
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The definition of ring A as a 5-6 membered cyclic ring and Ar as arylene, heteroarylene or a heterocyclic group is too broadly formulated to permit an adequate search. The search has essentially been limited to compounds that are supported by the examples.

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00569

Claims 74-77 relate to methods of treatment of the human or animal body by surgery or by therapy./diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/DK 99/00569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9919313 A1	22/04/99	NONE	
WO 9604260 A1	15/02/96	AP 9700918 D	00/00/00
		AU 697545 B	08/10/98
		AU 1006199 A	04/03/99
		AU 3382695 A	04/03/96
		BG 101180 A	30/04/98
		BR 9508468 A	25/11/97
		CA 2196079 A	15/02/96
		CN 1158123 A	27/08/97
		CZ 9700254 A	17/09/97
		EP 0772605 A	14/05/97
		FI 970357 A	26/03/97
		GB 9415330 D	00/00/00
		HU 76637 A	28/10/97
		IL 114759 D	00/00/00
		IL 125525 D	00/00/00
		JP 10503508 T	31/03/98
		NO 970373 A	18/03/97
		NZ 292125 A	25/11/98
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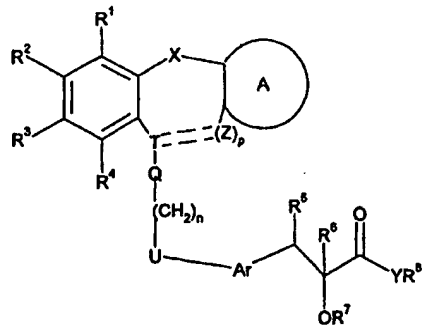

(Ia)

(57) Abstract

The present invention relates to compounds of general formula (Ia). The compounds are useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator–Activated Receptors (PPAR).

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New Compounds, their Preparation and Use

FIELD OF INVENTION

The present invention relates to novel compounds, pharmaceutical compositions containing them, methods for preparing the compounds and their use as medicaments. More specifically, compounds of the invention can be utilised in the treatment of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR). The present compounds reduce blood glucose and triglyceride levels and are accordingly useful for the treatment of ailments and disorders such as diabetes and obesity.

The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

The compounds are useful for the treatment and/or prophylaxis of insulin resistance (type 2 diabetes), impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, hyperglycaemia, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders. The compounds of the present invention are also useful for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis. These compounds may also be useful for improving cognitive functions in dementia, treating diabetic complications, psoriasis, polycystic ovarian syndrome (PCOS) and prevention and treatment of bone loss, e.g. osteoporosis.

BACKGROUND OF THE INVENTION

Coronary artery disease (CAD) is the major cause of death in type 2 diabetic and metabolic syndrome patients (i.e. patients that fall within the 'deadly quartet' category of impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

The hypolipidaemic fibrates and antidiabetic thiazolidinediones separately display moderately effective triglyceride-lowering activities although they are neither potent nor efficacious enough to be a single therapy of choice for the dyslipidaemia often observed in type 2 diabetic or metabolic syndrome patients. The thiazolidinediones also potently lower circulating glucose levels of type 2 diabetic animal models and humans. However, the fibrate class of compounds are without beneficial effects on glycaemia. Studies on the molecular actions of these compounds indicate that thiazolidinediones and fibrates exert their action by activating distinct transcription factors of the peroxisome proliferator activated receptor (PPAR) family, resulting in increased and decreased expression of specific enzymes and apolipoproteins respectively, both key-players in regulation of plasma triglyceride content. Fibrates, on the one hand, are PPARα activators, acting primarily in the liver. Thiazolidinediones, on the other hand, are high affinity ligands for PPARγ acting primarily on adipose tissue.

Adipose tissue plays a central role in lipid homeostasis and the maintenance of energy balance in vertebrates. Adipocytes store energy in the form of triglycerides during periods of nutritional affluence and release it in the form of free fatty acids at times of nutritional deprivation. The development of white adipose tissue is the result of a continuous differentiation process throughout life. Much evidence points to the central role of PPARγ activation in initiating and regulating this cell differentiation. Several highly specialised proteins are induced during adipocyte differentiation, most of them being involved in lipid storage and metabolism. The exact link from activation of PPARγ to changes in glucose metabolism, most notably a decrease in insulin resistance in muscle, has not yet been clarified. A possible link is via free fatty acids such that activation of PPARγ induces Lipoprotein Lipase (LPL), Fatty Acid Transport Protein (FATP) and Acyl-CoA Synthetase (ACS) in adipose tissue but not in muscle tissue. This, in turn, reduces the concentration of free fatty acids in plasma dramatically, and due to substrate competition at the cellular level, skeletal muscle and other tissues with high metabolic rates eventually switch from fatty acid oxidation to glucose oxidation with decreased insulin resistance as a consequence.

PPARα is involved in stimulating β-oxidation of fatty acids. In rodents, a PPARα-mediated change in the expression of genes involved in fatty acid metabolism lies at the basis of the phenomenon of peroxisome proliferation, a pleiotropic cellular response, mainly limited to liver and kidney and which can lead to hepatocarcinogenesis in rodents. The phenomenon of peroxisome proliferation is not seen in man. In addition to its role in peroxisome

proliferation in rodents, PPARα is also involved in the control of HDL cholesterol levels in rodents and humans. This effect is, at least partially, based on a PPARα-mediated transcriptional regulation of the major HDL apolipoproteins, apo A-I and apo A-II. The hypotriglyceridemic action of fibrates and fatty acids also involves PPARα and can be summarised as follows: (I) an increased lipolysis and clearance of remnant particles, due to changes in lipoprotein lipase and apo C-III levels, (II) a stimulation of cellular fatty acid uptake and their subsequent conversion to acyl-CoA derivatives by the induction of fatty acid binding protein and acyl-CoA synthase, (III) an induction of fatty acid b-oxidation pathways, (IV) a reduction in fatty acid and triglyceride synthesis, and finally (V) a decrease in VLDL production. Hence, both enhanced catabolism of triglyceride-rich particles as well as reduced secretion of VLDL particles constitutes mechanisms that contribute to the hypolipidemic effect of fibrates.

A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (U.S. Pat. 5,306,726, PCT Publications nos. W091/19702, WO 95/03038, WO 96/04260, WO 94/13650, WO 94/01420, WO 97/36579, WO 97/25042, WO 95/17394, WO 99/08501, WO 99/19313 and WO 99/16758).

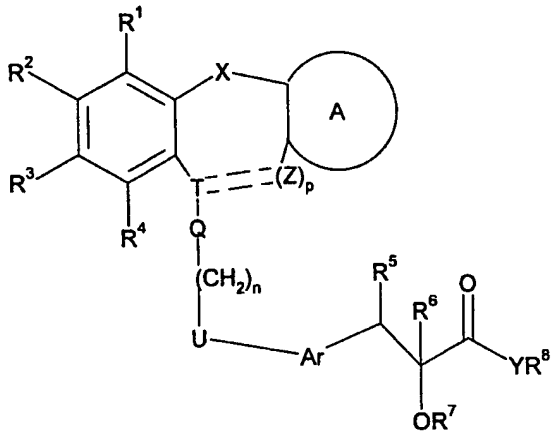
SUMMARY OF THE INVENTION

It seems more and more apparent that glucose lowering as a single approach does not overcome the macrovascular complications associated with type 2 diabetes and metabolic syndrome. Novel treatments of type 2 diabetes and metabolic syndrome must therefore aim at lowering both the overt hypertriglyceridaemia associated with these syndromes as well as alleviation of hyperglycaemia.

The clinical activity of fibrates and thiazolidinediones indicates that research for compounds displaying combined PPAR α and PPAR γ activation should lead to the discovery of efficacious glucose and triglyceride lowering drugs that have great potential in the treatment of type 2 diabetes and the metabolic syndrome (i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (Ia):



(Ia)

wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-12}alkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, halogen, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

or R^1 and R^2, R^2 and R^3 and/or R^3 and R^4 may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C_{1-6}alkyl;

ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy,

hydroxyC_{1-12}alkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, halogen, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

X is a valence bond, -(CHR^9)-, -(CHR^9)-CH_2-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH_2-, -(CHR^9)-CH=CH-, -(CHR^9)-CH_2-CH_2-, -(C=O)-, -O-CH_2-O-, -(NR^9)-, -(NR^9)-S(O_2)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH_2-(SO)-, -S-, -(SO)-, -(SO_2)-, -CH_2-(SO_2)-, -CH_2-O-CH_2-, wherein R^9 is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C_{1-12}alkyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{13}, or -SO_2R^{14}, wherein R^{13} and R^{14} independently of each other are selected from hydroxy, halogen, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl;

T is >N-, >CH-, >C<, -CH_2-N<,

Z is -CH_2-, =CH-, >N-, -O-, -S-, >CO, >SO, >SO_2, >NR^{15}, wherein R^{15} is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C_{1-12}alkyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{16}, or -SO_2R^{17}, wherein R^{16} and R^{17} independently of each other are selected from hydroxy, halogen, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl;

Q is -O-, -S-, >NR^{18}, wherein R^{18} is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C_{1-12}alkyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C_{1-12}alkyl-

amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, $-COR^{19}$, or $-SO_2R^{20}$, wherein R^{19} and R^{20} independently of each other are selected from hydroxy, halogen, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl;

U is -O-, -S-, $>SO_2$, $>NR^{21}$, wherein R^{21} is hydrogen or C_{1-6}alkyl,

$T==(Z)_p$ represents a single bond or a double bond,

Ar represents arylene, heteroarylene, or a divalent heterocyclic group optionally substituted with one or more C_{1-6}alkyl or aryl;

R^5 represents hydrogen, hydroxy, halogen, C_{1-12}alkoxy, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R^5 forms a bond together with R^6,

R^6 represents hydrogen, hydroxy, halogen, C_{1-12}alkoxy, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, acyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R^6 forms a bond together with R^5,

R^7 represents hydrogen, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, aryl, aralkyl, C_{1-12}alkoxyC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, C_{1-12}alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

R^8 represents hydrogen, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

Y represents oxygen, sulphur or NR^{10}, where R^{10} represents hydrogen, C_{1-12}alkyl, aryl, hydroxyC_{1-12}alkyl or aralkyl groups or when Y is NR^{10}, R^8 and R^{10} may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C_{1-6}alkyl;

n is an integer ranging from 1 to 4,

p is an integer ranging from 0 to 1,

or a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, het-

eroaralkoxy, acyl, acyloxy, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R^1 and R^2, R^2 and R^3 and/or R^3 and R^4 may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C_{1-6}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino or aralkoxycarbonylamino.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, C_{1-7}alkyl-amino, arylamino, aralkylamino, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alky or C_{1-7}alkylthio.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl, aralkyl, hydroxyC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl or aralkoxyC_{1-7}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen or C_{1-7}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^1, R^2, R^3, and R^4 represent hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, $-COR^{11}$, or $-SO_2R^{12}$, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy or cyano.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino or aralkoxycarbonylamino.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, C_{1-7}alkyl-amino, arylamino, aralkylamino, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl or C_{1-7}alkylthio.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl or C_{1-7}alkyl, C_{4-7}-

alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aralkyl, hydroxyC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl or aralkoxyC_{1-7}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 6 membered cyclic ring, optionally substituted with one or more chlorine or methyl groups.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represent a phenyl ring.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(CHR^9)-CH=CH-, -(CHR^9)-CH$_2$-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-S(O$_2$)-, -(NR^9)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)- or -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen, halogen, hydroxy, C_{1-7}alkyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, hydroxyalkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-12}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-12}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino or aralkoxycarbonylamino.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(CHR^9)-CH=CH-, -(CHR^9)-CH$_2$-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-S(O$_2$)-, -(NR^9)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)- or -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen, halogen, hydroxy, C_{1-7}alkyl, aryl, aralkyl, C_{1-7}alkoxyC_{1-12}alkyl, aryloxyC_{1-7}alkyl or aralkoxyC_{1-7}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(CHR^9)-CH=CH-, -(CHR^9)-CH$_2$-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-S(O$_2$)-, -(NR^9)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)- or -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -O-CH$_2$-O-, -(NR^9)-, -S-, -(SO)- or -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -O-CH$_2$-O-, -(NR^9)-, -S- or -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -O-CH$_2$-O- or -S-, wherein R^9 is hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -S-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T is >C<.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is -CH$_2$-, =CH-, >N-, -O-, -S-, >CO, >SO, >SO$_2$.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is >N-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is -O-, -S-, >NR^{18}, wherein R^{18} is hydrogen or C$_{1-7}$alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is >NR^{18}, wherein R^{18} is hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein U is -O-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T==$(Z)_p$ represents a double bond.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene optionally substituted with one or more C_{1-6}alkyl or aryl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents phenyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^5 represents hydrogen, hydroxy, halogen, C_{1-7}alkoxy, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl or aralkyl, or R^5 forms a bond together with R^6.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^5 represents hydrogen or R^5 forms a bond together with R^6.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^5 represents hydrogen, hydroxy, halogen, C_{1-7}alkoxy, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl or aralkyl, or R^5 forms a bond together with R^6.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^5 represents hydrogen or R^5 forms a bond together with R^6.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^7 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl, aralkyl, C_{1-7}alkoxyC_{1-7}alkyl, C_{1-7}alkoxycarbonyl, aryloxycarbonyl, C_{1-7}alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^7 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl or C_{2-7}-alkynyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^7 represents C_{1-2}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl or aralkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 represents hydrogen or C_{1-2}alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen, sulphur or NR^{10}, where R^{10} represents hydrogen, C_{1-7}alkyl, aryl, hydroxyC_{1-7}alkyl or aralkyl groups.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein n is an integer ranging from 2 to 3.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein p is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A is benzo.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -O-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -S-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is -S- and p is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is $-CH_2-$ and p is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is =CH- and p is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein $T==(Z)_p$ represents a single bond or a double bond.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T is >CH-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T is >C<.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is -O-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is -S-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is $>NR^{18}$, wherein R^{18} is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein n is 2.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein U is -O-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar is phenylene.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^5 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^6 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^7 is ethyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R^8 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein p is 0.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A is a five membered ring containing S.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is $-(CHR^9)-CH_2-$, wherein R^9 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is $-O-(CHR^9)-$, wherein R^9 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is $-S-(CHR^9)-$, wherein R^9 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -O-CH_2-O-.

Preferred compounds of the invention are:

2-Ethoxy-3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yloxy)-ethoxy]-phenyl}-propionic acid,

3-(4-[2-(Dibenzo[b,f]-1,4-thiazepin-11-ylamino)-ethoxy]-phenyl)-2-ethoxy-propinoic acid ethyl ester,

3-{4-[2-(Dibenzo[*b,f*][1,4]thiazepin-11-ylamino)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(10,11-Dihydro-dibenzo[*b,f*]thiepin-10-ylsulfanyl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-(4-[2-[5*H*-Dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,

3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,

3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid,

3-(4-[2-(6,11-Dihydrodibenzo[b,e]oxepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,

3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,

3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid,

2-Ethoxy-3-(4-[2-(2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-ethoxy]-phenyl)-propionic acid ethyl ester,

3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propanoic acid ethyl ester,

3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propanoic acid,

3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid ethyl ester,

3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid;

or a pharmaceutically acceptable salt thereof.

Further, preferred compounds of the invention are:

2-Ethoxy-3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yloxy)-ethoxy]-phenyl}-propionic acid,

3-{4-[2-(Dibenzo[*b,f*][1,4]thiazepin-11-ylamino)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(10,11-Dihydro-dibenzo[*b,f*]thiepin-10-ylsulfanyl)-ethoxy]-phenyl}-2-ethoxy-propionic acid;

or a pharmaceutically acceptable salt thereof.

In the above structural formulas and throughout the present specification, the following terms have the indicated meaning:

The terms "C_{1-12}-alkyl" as used herein, alone or in combination is intended to include those alkyl groups of the designated length in either a linear or branched or cyclic configuration. represents e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like. Typical C_{1-6}-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, hexyl, iso-hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

The terms "$C_{2-n'}$-alkenyl" wherein n' can be from 3 through 15, as used herein, represents an olefinically unsaturated branched or straight group having from 2 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-proppenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl, and the like.

The terms "$C_{2-n'}$-alkynyl" wherein n' can be from 3 through 15, as used herein, represent an unsaturated branched or straight group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl and the like.

The terms "$C_{4-n'}$-alkenynyl" wherein n' can be from 5 through 15, as used herein, represent an unsaturated branched or straight hydrocarbon group having from 4 to the specified number of carbon atoms and both at least one double bond and at least one triple bond. Examples of such groups include, but are not limited to, 1-penten-4-yne, 3-penten-1-yne, 1,3-hexadiene-5-yne and the like.

The term "C_{1-12}-alkoxy" as used herein, alone or in combination is intended to include those C_{1-12}-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked thorugh an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isoprpoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Example of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The term "C_{1-6}-alkoxycarbonyloxy" is intended to include the above defined C_{1-6}-alkoxy groups attached to a carbonyloxy moiety, eg. methoxycarbonyloxy, ethoxycarbonyloxy, etc..

As used herein the term "C_{4-12}-(cycloalkylalkyl)" represents a branched or straight alkyl group substituted at a carbon with a cycloalkyl group. Examples of such groups include, but are not limited to, cyclopropylethyl, cyclobutylmethyl, 2-(cyclohexyl)ethyl, cyclohexylmethyl, 3-(cyclopentyl)-1-propyl, and the like.

The term "C_{1-12}-alkylthio" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C_{1-12}-alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 12 carbon atoms e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio. Example of cyclic alkylthio are cyclopropylthio, cyclobutylthio, cyclopentylthio and cyclohexylthio.

The term "C_{1-12}alkylamino" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C_{1-12}-alkyl group linked through amino having a free valence bond from the nitrogen atom e.g. methylamino, ethylamino, propylamino, butylamino, pentylamino. Example of cyclic alkylamino are cyclopropylamino, cyclobutylamino, cyclopentylamino and cyclohexylamino.

The term "hydroxyC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached a hydroxy group, e.g. hydroxyethyl,. 1-hydroxypropyl, 2-hydroxypropyl etc..

The term "arylamino" as used herein, alone or in combination, refers to an aryl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. phenylamino, naphthylamino, etc..

The term "aralkylamino" as used herein, alone or in combination, refers to an aralkyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. benzylamino, phenethylamino, 3-phenylpropylamino, 1-naphtylmethylamino, 2-(1-naphtyl)ethylamino and the like.

The term "aminoC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached an amino group, e.g. aminoethyl, 1-aminopropyl, 2-aminopropyl etc..

The term "aryloxycarbonyl" as used herein, alone or in combination, refers to an aryloxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. phenoxycarbonyl, 1-naphthyloxycarbonyl or 2-naphthyloxycarbonyl, etc..

The term "aralkoxycarbonyl" as used herein, alone or in combination, refers to an aralkoxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. benzyloxycarbonyl, phenethoxycarbonyl, 3-phenylpropoxycarbonyl, 1-naphthylmethoxycarbonyl, 2-(1-naphtyl)ethoxycarbonyl, etc..

The term "C_{1-12}alkoxyC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached a C_{1-12}alkoxy as defined herein, e.g. methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, etc..

The term "aryloxyC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached an aryloxy as defined herein, e.g. phenoxymethyl, phenoxydodecyl, 1-naphthyloxyethyl, 2-naphthyloxypropyl, etc..

The term "aralkoxyC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached an aralkoxy as defined herein, e.g. benzyloxymethyl, phenethoxydodecyl, 3-phenylpropoxyethyl, 1-naphthylmethoxypropyl, 2-(1-naphtyl)ethoxymethyl, etc..

The term "thioC_{1-12}alkyl" as used herein, alone or in combination, refers to a C_{1-12}alkyl as defined herein whereto is attached a group of formula -SR"' wherein R"' is hydrogen, C_{1-6}alkyl or aryl, e.g. thiomethyl, methylthiomethyl, phenylthioethyl, etc..

The term "C_{1-12}alkoxycarbonylamino" as used herein, alone or in combination, refers to a C_{1-12}alkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. methoxycarbonylamino, carbethoxyamino, propoxycarbonylamino, isopropoxycarbonylamino, n-butoxycarbonylamino, tert-butoxycarbonylamino, etc..

The term "aryloxycarbonylamino" as used herein, alone or in combination, refers to an aryloxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. phenoxycarbonylamino, 1-naphthyloxycarbonylamino or 2-naphthyloxycarbonylamino, etc..

The term "aralkoxycarbonylamino" as used herein, alone or in combination, refers to an aralkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. benzyloxycarbonylamino, phenethoxycarbonylamino, 3-phenylpropoxycarbonylamino, 1-naphthylmethoxycarbonylamino, 2-(1-naphtyl)ethoxycarbonylamino, etc..

The term "aryl" is intended to include aromatic rings, such as carboxylic aromatic rings selected from the group consisting of phenyl, naphthyl, (1-naphtyl or 2-naphtyl) optionally substituted with halogen, amino, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy.

The term "arylene" is intended to include divalent aromatic rings, such as carboxylic aromatic rings selected from the group consisting of phenylene, naphthylene, optionally substituted with halogen, amino, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "perhalomethyl" means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

The term "C_{1-6}-dialkylamino" as used herein refers to an amino group wherein the two hydrogen atoms independently are substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-pentyl)amino, and the like.

The term "acyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-alkyl group linked through a carbonyl group; such as e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl, and the like.

The term "acyloxy" as used herein refers to acyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy, valeryloxy, and the like.

The term "C_{1-12}-alkoxycarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-12}-alkoxy group linked through a carbonyl group; such as e.g. methoxycarbonyl, carbethoxy, propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 3-methylbutoxycarbonyl, n-hexoxycarbonyl and the like.

The term "a cyclic ring containing from 5 to 7 carbon atoms" as used herein refers to a monocyclic saturated or unsaturated or aromatic system, wherein the ring may be cyclopentyl, cyclopentenyl, cyclohexyl, phenyl or cycloheptyl.

The term "bicycloalkyl" as used herein refers to a monovalent substituent comprising a bicyclic structure made of 6-12 carbon atoms such as e.g. 2-norbornyl, 7-norbornyl, 2-bicyclo[2.2.2]octyl and 9-bicyclo[3.3.1]nonanyl.

The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole,

quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine.

The term "heteroarylene" as used herein, alone or in combination, refers to a divalent group comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine.

The term "heteroaryloxy" as used herein, alone or in combination, refers to a heteroaryl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine linked to oxygen.

The term "aralkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphtylmethyl, 2-(1-naphtyl)ethyl and the like.

The term "aryloxy" as used herein refers to phenoxy, 1-naphthyloxy or 2-naphthyloxy.

The term "aralkoxy" as used herein refers to a C_{1-6}-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphtyl)ethoxy and the like.

The term "heteroaralkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with a heteroaryl group; such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like.

The term "heteroaralkoxy" as used herein refers to a heteroaralkyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom, e.g. (2-furyl)methyl,

(3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl linked to oxygen.

The term "C_{1-6}-alkylsulfonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-alkyl group linked through a sulfonyl group such as e.g. methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, n-hexylsulfonyl, 4-methylpentylsulfonyl, neopentylsulfonyl, n-hexylsulfonyl and 2,2-dimethylpropylsulfonyl.

The term "C_{1-6}-monoalkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-monoalkylamino group linked through a sulfonyl group such as e.g. methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, isopropylaminosulfonyl, n-butylaminosulfonyl, sec-butylaminosulfonyl, isobutylaminosulfonyl, tert-butylaminosulfonyl, n-pentylaminosulfonyl, 2-methylbutylaminosulfonyl, 3-methylbutylaminosulfonyl, n-hexylaminosulfonyl, 4-methylpentylaminosulfonyl, neopentylaminosulfonyl, n-hexylaminosulfonyl and 2,2-dimethylpropylaminosulfonyl.

The term "C_{1-6}-dialkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-dialkylamino group linked through a sulfonyl group such as dimethylaminosulfonyl, N-ethyl-N-methylaminosulfonyl, diethylaminosulfonyl, dipropylaminosulfonyl, N-(n-butyl)-N-methylaminosulfonyl, di(n-pentyl)aminosulfonyl, and the like.

The term "C_{1-6}-alkylsulfinyl" as used herein refers to a monovalent substituent comprising a straight or branched C_{1-6}-alkyl group linked through a sulfinyl group (-S(=O)-); such as e.g. methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl, and the like.

The term "acylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with an acyl group, such as e.g. acetamido, propionamido, isopropylcarbonylamino, and the like.

The term "(C_{3-6}-cycloalkyl)C_{1-6}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms and being monosubstituted with a C_{3-6}-cycloalkyl group, the cycloalkyl group optionally being mono- or polysubsti-

tuted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. cyclopropylmethyl, (1-methylcyclopropyl)methyl, 1-(cyclopropyl)ethyl, cyclopentylmethyl, cyclohexylmethyl, and the like.

The term "arylthio" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; e.g. phenylthio, (4-methylphenyl)- thio, (2-chlorophenyl)thio, and the like.

The term "arylsulfinyl" as used herein refers to an aryl group linked through a sulfinyl group (-S(=O)-), the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. phenylsulfinyl, (4-chlorophenyl)sulfinyl, and the like.

The term "arylsulfonyl" as used herein refers to an aryl group linked through a sulfonyl group, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. phenylsulfonyl, tosyl, and the like.

The term "C_{1-6}-monoalkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-monoalkylamino group linked through a carbonyl group such as e.g. methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl, sec-butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, 2-methylbutylaminocarbonyl, 3-methylbutylaminocarbonyl, n-hexylaminocarbonyl, 4-methylpentylaminocarbonyl, neopentylaminocarbonyl, n-hexylaminocarbonyl and 2-2-dimethylpropylaminocarbonyl.

The term "C_{1-6}-dialkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-dialkylamino group linked through a carbonyl group such as dimethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, N-(n-butyl)-N-methylaminocarbonyl, di(n-pentyl)aminocarbonyl, and the like.

The term "C_{1-6}-monoalkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C_{1-6}-monoalkylaminocarbonyl group, e.g. methylaminocarbonylamino, ethylamino-carbonylamino, n-propylaminocarbonylamino, isopropylaminocarbonylamino, n-butylaminocarbonylamino, sec-butylaminocarbonylamino,

isobutylaminocarbonylamino, tert-butylaminocarbonylamino, and 2-methylbutylaminocarbonylamino.

The term "C_{1-6}-dialkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C_{1-6}-dialkylaminocarbonyl group, such as dimethylaminocarbonylamino, N-ethyl-N-methylaminocarbonylamino, diethylaminocarbonylamino, dipropylaminocarbonylamino, N-(n-butyl)-N-methylaminocarbonylamino, di(n-pentyl)aminocarbonylamino, and the like.

As used herein, the phrase "heterocyclyl" means a monovalent saturated or unsaturated group being monocyclic and containing one or more, such as from one to four carbon atom(s), and from one to four N, O or S atom(s) or a combination thereof. The phrase "heterocyclyl" includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. pyrrolidine, pyrroline); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofurazan); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms.

As used herein, the phrase "a divalent heterocyclic group" means a divalent saturated or unsaturated system being monocyclic and containing one or more, such as from one to four carbon atom(s), and one to four N, O or S atom(s) or a combination thereof. The phrase a divalent heterocyclic group includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. pyrrolidine, pyrroline); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofurazan); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms.

As used herein, the phrase "a 5-6 membered cyclic ring" means an unsaturated or saturated or aromatic system containing one or more carbon atoms and optionally from one to four N, O or S atom(s) or a combination thereof. The phrase "a 5-6 membered cyclic ring" includes, but is not limited to, e.g. cyclopentyl, cyclohexyl, phenyl, cyclohexenyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiomorpholinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl, 1,4-dioxolanyl, 5-membered heterocycles having one hetero atom (e.g. thiophenes, pyrroles, furans); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. oxazoles, pyrazoles, imidazoles, thiazoles, purines); 5-membered heterocycles having three heteroatoms (e.g. triazoles, thiadiazoles); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. pyridine, quinoline, isoquinoline, phenanthridine, cyclohepta[b]pyridine); 6-membered heterocycles with two heteroatoms (e.g. pyridazines, cinnolines, phthalazines, pyrazines, pyrimidines, quinazolines, morpholines); 6-membered heterocycles with three heteroatoms (e.g. 1,3,5-triazine); and 6-membered heterocycles with four heteroatoms.

As used herein, the phrase "5- or 6-membered nitrogen containing ring" refers to a monovalent substituent comprising a monocyclic unsaturated or saturated or aromatic system containing one or more carbon, nitrogen, oxygen or sulfur atoms or a combination thereof and having 5 or 6 members, e.g. pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiomorpholinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl and 1,4-dioxolanyl.

Certain of the above defined terms may occur more than once in the above formula (Ia), and upon such occurence each term shall be defined independently of the other.

Pharmaceutically acceptable salts forming part of this invention include salts of the carboxylic acid moiety such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succi-

nates, palmoates, methanesulplionates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

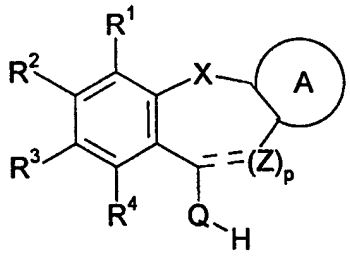
The pharmaceutically acceptable salts are prepared by reacting the compound of formula (Ia) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents lilke ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guandine and their derivatives etc. may also be used. Alternatively, acid addition salts whereever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (Ia) may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (Ia) may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of compound of general formula (Ia) forming part of this invention may be prepared by crystallization of compound of formula (Ia) under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

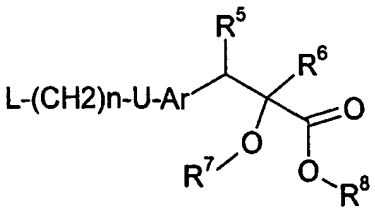
The invention also relate to methods of preparing the above mentioned compounds, comprising:

a) reacting a compound of formula II



II

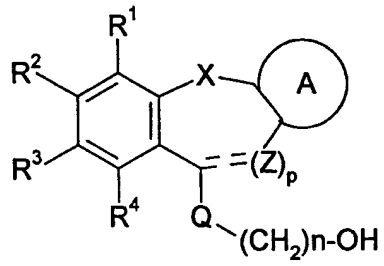
wherein R^1-R^4, A, X, Z, p and Q are defined as above, with a compound of formula III



III

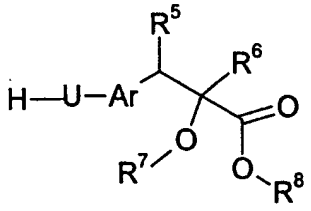
wherein L is a leaving group such as halogen, p-toluenesulfonate, methanesulfonate and the like and wherein n, U, Ar, R^5-R^8 are defined as above except that R^8 is not H, to obtain a compound of formula (Ia) wherein n, p, Ar, R^1-R^8, A, X, Z, U and Q are defined as above except that R^8 is not H.

b) reacting a compound of formula IV



IV

wherein R^1-R^4, A, X , Z, Q, p and n are defined as above, with a compound of formula V

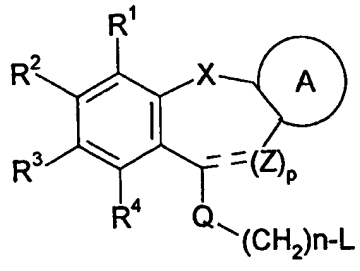


V

wherein U, Ar and R^5-R^8 are defined as above except that R^8 is not H, by using suitable coupling agents such as dicyclohexyl urea, triarylphosphine/ dialkylazadicarboxylate such as PPh_3/ DEAD (Diethylazodicarboxylate) and the like, to obtain a compound of formula I, wherein n, p, Ar, R^1-R^8, A, X , Z, U

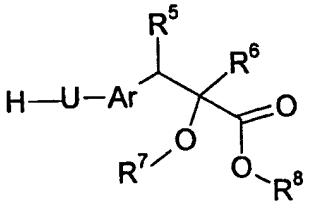
and Q are defined as above except that R^8 is not H, and U is not C.

c) reacting a compound of formula VI



VI

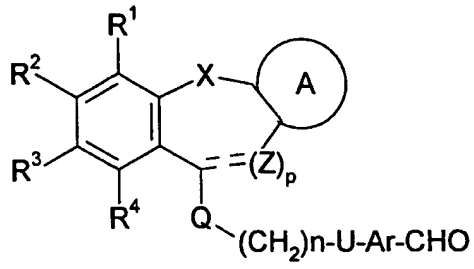
wherein L is a leaving group such as halogen, p-toluenesulfonate, methanesulfonate and the like and wherein R^1-R^4, A, X ,Z, Q, p and n are defined as above, with an compound of formula V



V

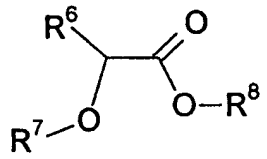
wherein U, Ar and R^5-R^8 are defined as above except that R^8 is not H, to obtain a compound of formula (Ia) wherein n, p, Ar, R^1-R^8, A, X, Z, U and Q are defined as above except that R^8 is not H and U is not C.

d) reacting a compound of formula VII



VII

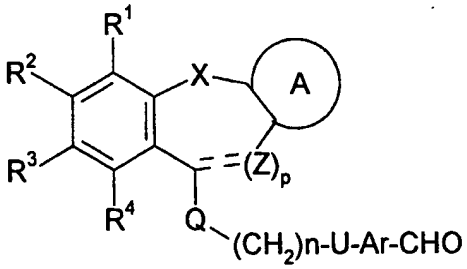
wherein R^1-R^4, A, X, Z, Q, U, Ar, p, and n are defined as above, with an compound of formula VIII



VIII

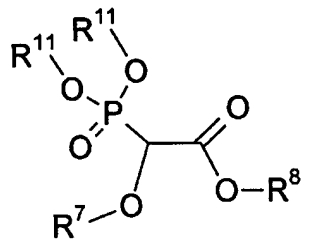
wherein R^6-R^8 are defined as above except that R^8 is not H, to obtain the β-hydroxy aldol product, which may be dehydroxylated or dehydrated to obtain a compound of formula (Ia) wherein n, p, Ar, R^1-R^8, A, X, Z, U and Q are defined as above except that R^8 is not H.

e) reacting a compound of formula VII



VII

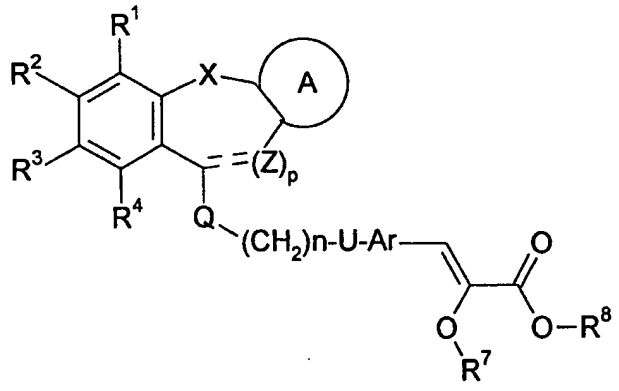
wherein R^1-R^4, A, X, Q, Z, U, Ar, p and n are defined as above, with an compound of formula IX



IX

wherein R^7 and R^8 are defined as above except that R^8 is not H, and wherein R^{11} is a lower alkyl group to obtain a compound of formula (Ia) wherein n, p, Ar, R^1-R^4, R^7- R^8, A, X, Z , U and Q are defined as above except that R^8 is not H and wherein R^5 forms a bond together with R^6 .

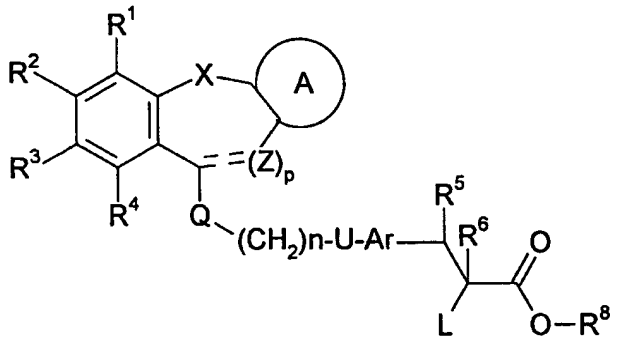
f) hydrogenation of a compound of formula X



X

wherein n, p, Ar, R^1-R^4, R^7-R^8, A, X , Z , U and Q are defined as above except that R^8 is not H, to obtain a compound of formula (Ia) wherein n, p, Ar, R^1-R^4, R^7- R^8, A, X, Z, U and Q are defined as above except that R^8 is not H and wherein R^5 and R^6 is hydrogen.

g) reacting a compound of formula XI



XI

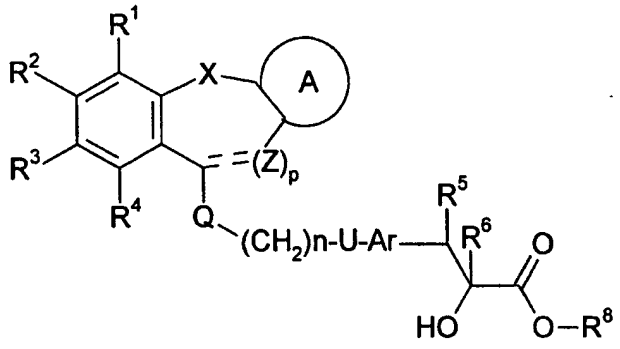
wherein L is a leaving group such as halogen and R^1-R^8, A, X , Q, Z, U, p and n are defined as above except that R^8 is not H, with an alcohol of formula XII

$$HO-R^7$$

XII

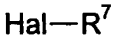
wherein R^7 is defined as above, to obtain a compound of formula (Ia) wherein n, p, Ar, R^1-R^8, R^7, A, X, Z , U and Q is defined as above except that R^8 is not H.

h) reacting a compound of formula XIII



XIII

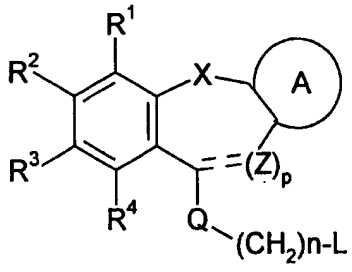
wherein n, p, Ar, R^1-R^6, A, X, Z, U and Q is defined as above and wherein R^8 is defined as above except that R^8 is not H, with a compound of formula XIV



XIV

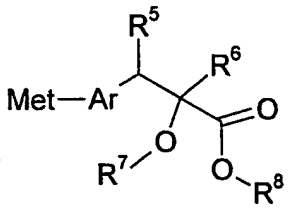
wherein R^7 is defined as above and wherein "Hal" represents Cl, Br, or I to obtain a compound of formula (Ia) wherein n, p, Ar, R^1- R^8, A, X , Z, U and Q is defined as above except that R^8 is not H.

i) reacting a compound of formula VI



VI

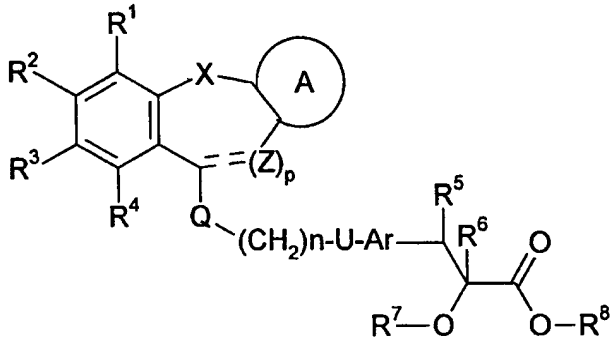
wherein L is a leaving group such as halogen, p-toluenesulfonate, methanesulfonate and the like and wherein R^1-R^4, A, X , Q, Z, p and n are defined as above, with a nucleophilic compound of formula XV



XV

wherein "Met" is a metal such as zinc or copper, carrying suitable ligands chosen preferentially from trifluoro-methanesulfonate, halide or C_1-C_6 alkyl, to obtain a compound of formula (Ia) wherein n, p, Ar, R^1-R^8, R^7, A, X and Q is defined as above except that R^8 is not H, and U is C.

j) saponification a compound of formula XVI



XVI

wherein n, p, Ar, R^1-R^8, A, X , Z, U and Q is defined as above except that R^8 is not H, to obtain a compound of formula (Ia) wherein n, Ar, R^1-R^7, A, X, Z and Q is defined as above and wherein R^8 is H.

The starting materials are commercially available or readily prepared by methods familiar to those skilled in the art.

PHARMACOLOGICAL METHODS

In vitro PPAR alpha and PPAR gamma activation activity.

Principle

The PPAR gene transcription activation assays were based on transient transfection into human HEK293 cells of two plasmids encoding a chimeric test protein and a reporter protein respectively. The chimeric test protein was a fusion of the DNA binding domain (DBD) from the yeast GAL4 transcription factor to the ligand binding domain (LBD) of the human PPAR proteins. The PPAR LBD harbored in addition to the ligand binding pocket also the native activation domain (activating function 2 = AF2) allowing the fusion protein to function as a PPAR ligand dependent transcription factor. The GAL4 DBD will force the fusion protein to bind only to Gal4 enhancers (of which none existed in HEK293 cells). The reporter plasmid contained a Gal4 enhancer driving the expression of the firefly luciferase protein. After transfection, HEK293 cells expressed the GAL4-DBD-PPAR-LBD fusion protein. The fusion protein will in turn bind to the Gal4 enhancer controlling the luciferase expression, and do nothing in the absence of ligand. Upon addition to the cells of a PPAR ligand, luciferase protein will be produced in amounts corresponding to the activation of the PPAR protein. The amount of luciferase protein is measured by light emission after addition of the appropriate substrate.

Methods

Cell culture and transfection: HEK293 cells were grown in DMEM + 10% FCS, 1% PS. Cells were seeded in 96-well plates the day before transfection to give a confluency of 80 % at transfection. 0,8 µg DNA per well was transfected using FuGene transfection reagent according to the manufacturers instructions (Boehringer-Mannheim). Cells were allowed to express protein for 48 h followed by addition of compound.

Plasmids: Human PPAR α and γ was obtained by PCR amplification using cDNA templates from liver, intestine and adipose tissue respectively. Amplified cDNAs were cloned into pCR2.1 and sequenced. The LBD from each isoform PPAR was generated by PCR (PPARα: aa 167 - C-term; PPARγ: aa 165 - C-term) and fused to GAL4-DBD by subcloning fragments in frame into the vector pM1 generating the plasmids pM1αLBD and pM1γLBD. Ensuing fusions were verified by sequencing. The reporter was constructed by inserting an oligonucleotide encoding five repeats of the Gal4 recognition sequence into the pGL2 vector (Promega).

Compounds: All compounds were dissolved in DMSO and diluted 1:1000 upon addition to the cells. Cells were treated with compound (1:1000 in 200 µl growth medium including de-lipidated serum) for 24 h followed by luciferase assay.

Luciferase assay: Medium including test compound was aspirated and 100 µl PBS incl. 1mM Mg++ and Ca++ was added to each well. The luciferase assay was performed using the Lu-cLite kit according to the manufacturers instructions (Packard Instruments). Light emission was quantified by counting SPC mode on a Packard Instruments top-counter.

PHARMACEUTICAL COMPOSITIONS

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the general formula (Ia) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of formula (Ia) or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which

may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin

capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula (Ia) dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	5 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	Ad.
Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases related to the regulation of blood sugar.

Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a dosage of from about 2 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.001 mg to about 100 mg, preferably from about 0.01 mg to about 50 mg of the compounds of formula (Ia) admixed with a pharmaceutically acceptable carrier or diluent.

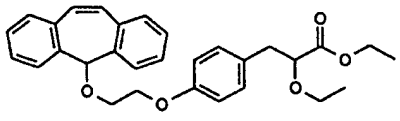
In a further aspect, the present invention relates to a method of treating and/or preventing type I or type II diabetes.

In a still further aspect, the present invention relates to the use of one or more compounds of the general formula (Ia) or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment and/or prevention of type I or type II diabetes.

Any novel feature or combination of features described herein is considered essential to this invention.

The invention will now be described in further detail with reference to the following examples. The examples are provided for illustrative purposes, and are not to be construed as limiting the scope of the invention in any way.

EXAMPLE 1



3-(4-[2-[5*H*-Dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester

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a)

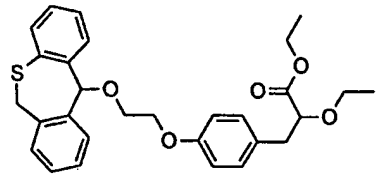
Dibenzosuberenol (2.08 g, 10 mmol) was dissolved in dry THF (20 mL) at 0 °C. Sodium hydride (1.0 g of 50 % mineral oil dispersion, 20 mmol) was added. After 10 min. *tert*-butylbromoacetate (4.0 g, 20.0 mmol) was added over a period of 20 min and then stirred for 1h. The reaction mixture was quenched with water at 0 °C and the product extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), and concentrated in vacuo. The product was redissolved in ether (20 mL) and added dropwise to an ether (15 mL) suspension of lithium aluminium hydride (190 mg, 5.0 mmol). The reaction was stirred 16 h at room temperature, quenched with water. The ether solution was washed with water, dried, and concentrated in vacuo to give 1.3 g (50%) of 2-(5*H*-dibenzo[a,d]cyclohepten-5-yloxy)-ethanol.

b)

Under a nitrogen atmosphere, 2-(5*H*-dibenzo[a,d]cyclohepten-5-yloxy)-ethanol (400 mg, 1.6 mmol), tributylphosphine (480 mg, 2.4 mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (380 mg, 1.6 mmol) were successively dissolved in dry benzene (10 mL). Solid azodicarboxylic dipiperidine (ADDP) (480 mg, 2.4 mmol) was added under stirring at 0 °C to the solution. After 10 min, the reaction mixture was brought to room temperature and

the stirring was continued for 2h. The mixture was added water and the product extracted with ethyl acetate. The combined organic phases was dried ($MgSO_4$), and concentrated in vacuo. The residue was purified chromatography eluting with ethyl acetate/hexane (1:9) to give 350 mg (47%) of the title compound: MS 472 (M^+).

EXAMPLE 2



3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester

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a)

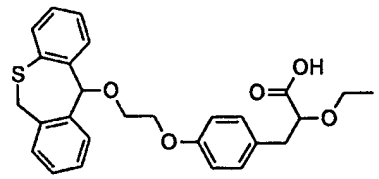
6,11-Dihydrodibenzo[b,e]thiepin-11-ol (1.14 g, 5 mmol) was dissolved in dry THF (25 mL) at 0 °C. Sodium hydride (0.24 g of 50 % mineral oil dispersion, 5 mmol) was added portion-wise at 0 °C and then refluxed for 30 min. *tert*-Butylbromoacetate (980 mg, 5.0 mmol) in dry THF (10 mL) was added over a period of 20 min followed by a 30 min reflux. The reaction mixture was quenched with water at 0 °C and the product extracted with ether. The combined extracts were dried ($MgSO_4$), and concentrated in vacuo. The product was redissolved in ether and added dropwise to an ether (15 mL) suspension of lithium aluminium hydride (190 mg, 5.0 mmol). The reaction was stirred 16 h at room temperature, quenched with water, cooled, and filtered through Decalit. The ether solution was washed with saturated NaCl, dried, and purified by chromatography eluting with ethyl acetate/dichloromethan (1:10) to give 850 mg (63%) of 2-(6,11-dihydrodibenzo[b,e]thiepin-11-yloxy)-ethanol. ^1H NMR (300 MHz, $CDCl_3$) δ 3.55-3.70 (m, 2H), 3.75-3.85 (m, 2H), 4.00 (bs,1H), 4.85 (bs, 1H), 5.55 (bs, 1H), 7.03-7.13 (m, 3H), 7.13-7.48 (m, 5H).

b)

Under a nitrogen atmosphere, 2-(6,11-dihydrodibenzo[b,e]thiepin-11-yloxy)-ethanol (340 mg, 1.25 mmol), tributylphosphine (280 mg, 1.37 mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-

propionic acid ethyl ester (330 mg, 1.37 mmol) were successively dissolved in dry benzene (10 mL). Solid azodicarboxylic dipiperidine (ADDP) (350 mg, 1.37 mmol) was added under stirring at 0 °C to the solution. After 10 min, the reaction mixture was brought to room temperature and the stirring was continued for 16 h. Heptane (10 mL) was added to the reaction mixture and dihydro-ADDP separated out was filtered off. After evaporation of the solvent the product was purified chromatography eluting with ethyl acetate/heptane (1:4) to give 460 mg (75%) of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H), 1.25 (t, 3H), 2.95 (d, 2H), 3.30-3.40 (m, 1H), 3.55-3.65 (m, 1H), 2.85 (t, 2H), 3.95 (t, 1H), 4.10-4.22 (m, 4H), 4.5-5.1 (bs, 1H), 5.60-5.75 (bs, 1H), 6.82 (d, 2H), 7.05-7.50 (m, 10H).

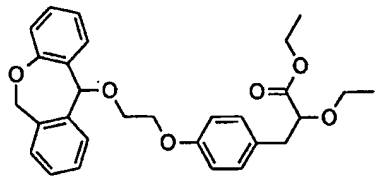
EXAMPLE 3



3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid

3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester (example 2) (220 mg, 0.44 mmol) in ethanol (5 mL) was added NaOH 1N (0.9 mL, 0.9 mmol).The mixture was stirred at room temperature for 16 h. The ethanol was evaporated of and pH adjusted with HCl 1N to pH 1. After extraction with dichloromethane the product was purified by chromatography, using dichloromethane/methanol (9:1) as eluent, to give 126 mg (62%) of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H), 2.85-3.10 (m, 2H), 3.32-3.42 (m, 1H), 3.52-3.65 (m, 1H), 2.85 (t, 2H), 3.95-4.05 (m, 1H), 4.10-4.22 (m, 2H), 4.5-5.1 (bs, 1H), 5.60-5.75 (bs, 1H), 6.82 (d, 2H), 7.05-7.50 (m, 10H).

EXAMPLE 4



3-(4-[2-(6,11-Dihydrodibenzo[b,e]oxepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester

a)

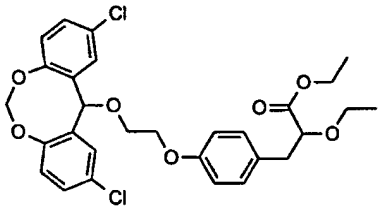
6,11-Dihydrodibenzo[b,e]oxepin-11-ol (1.06 g, 5 mmol) was dissolved in dry THF (25 mL) at 0 °C. Sodium hydride (0.24 g of 50 % mineral oil dispersion, 5 mmol) was added portion-wise at 0 °C and then refluxed for 30 min. *tert*-Butylbromoacetate (980 mg, 5.0 mmol) in dry THF (10 mL) was added over a period of 20 and the mixture stirred at 35 °C for 16h. The reaction mixture was quenched with water at 0 °C and the product extracted with ether. The combined extracts were dried ($MgSO_4$), and concentrated in vacuo. The product was redissolved in ether and added dropwise to an ether (15 mL) suspension of lithium aluminium hydride (190 mg, 5.0 mmol). The reaction was stirred 48 h at room temperature, quenched with water, cooled, and filtered through Decalit. The ether solution was washed with saturated NaCl, dried, and purified by chromatography eluting with ethyl acetate/dichloromethan (1:10) to give 267 mg (21%) of 2-(6,11-dihydrodibenzo[b,e]oxepin-11-yloxy)-ethanol.

b)

Under a nitrogen atmosphere, 2-(6,11-dihydrodibenzo[b,e]oxepin-11-yloxy)-ethanol (256 mg, 1.0 mmol), tributylphosphine (223 mg, 1.1 mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (262 mg, 1.1 mmol) were successively dissolved in dry benzene (10 mL). Solid azodicarboxylic dipiperidine (ADDP) (278 mg, 1.1 mmol) was added under stirring at 0 °C to the solution. After 10 min, the reaction mixture was brought to room temperature and the stirring was continued for 16 h. Heptane (10 mL) was added to the reaction mixture and dihydro-ADDP separated out was filtered off. After evaporation of the solvent the product was purified chromatography eluting with ethyl acetate/heptane (1:4) to give 175 mg (37%) of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H), 1.25 (t, 3H), 2.93

(d, 2H), 3.30-3.40 (m, 1H), 3.55-3.65 (m, 1H), 3.65-3.75 (m, 1H),3.78-3.88 (m,1H), 3.95 (t, 1H), 4.10 (t, 2H), 4.15 (q, 2H), 4.85 (d, 1H), 5.25 (s, 1H), 6.15 (d, 1H), 6.75 (d,2H), 6.85-6.95 (m, 2H), 7.10 (d, 2H), 7.15-7.40 (m, 6H).

EXAMPLE 5



3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester

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a)

To a solution of bis-(5-chloro-2-hydroxyphenyl)-methane (24.4 g, 90.7 mmol) in dry DMF (340 mL) was added diiodomethane (25.5 g, 95.0 mmol) and potassium carbonate (18.2 g, 132 mmol).The mixture was stirred at 105 °C for 16 h. The mixture was added to ice water (1200 mL) and stirred for 30 min. The product was isolated by filtration, and washed with water and suspended in a mixture of ethanol (200 mL) and 4N NaOH (50 mL). The mixture was heated at 80 °C for 1 h. The mixture was added to water (600 mL) and 21.45 g (84%) 2,10-dichloro-12H-dibenzo[d,g][1,3]-dioxocin was isolated by filtration.

b)

To a solution of 2,10-dichloro-12H-dibenzo[d,g][1,3]-dioxocin (21.4 g, 76.1 mmol) and N-bromosuccinimide (13.5 g, 76.1 mmol) in tetrachloromethane (275 mL) was added azo-bisisobutyronitrile (200 mg, 1.2 mmol). The mixture was heated at 80 °C for 24 h. Another 3 x azobisisobutyronitrile (200 mg, 1.2 mmol) was added within the 24 h. The mixture was filtrated and the solution phase concentrated in vacuo. The residue was added dichloromethane (30 mL) and ether (100 mL). The mixture was filtered and the solution phase concentraded in vacuo. The residue was submitted to flash chromatography eluting with

heptane/ethyl acetate (3:1) to give 7.4 g (27%) of 12-bromo-2,10-dichloro-12H-5,7-dioxa-dibenzo[a,d]cyclooctene.

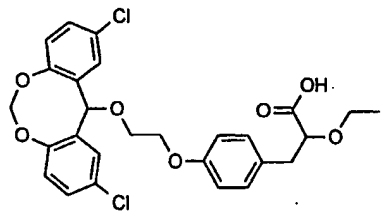
c)

A mixture of 12-bromo-2,10-dichloro-12H-5,7-dioxa-dibenzo[a,d]cyclooctene (900 mg, 2.5 mmol), 2-bromoethanol (3.75 g, 30 mmol) and potassium carbonate (1.0 g, 7.2 mmol) in dichloromethane (10 mL) was heated at 120 °C for 4 h. The reaction mixture was concentrated in vacuo, added water (25 mL) and the product extracted with ethyl acetate (3 x 25 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated to give 832 mg (82%) of 12-(2-bromo-ethoxy)-2,10-dichloro-12H-5,7-dioxa-dibenzo[a,d]cyclooctene.

d)

To a solution of12-(2-bromo-ethoxy)-2,10-dichloro-12H-5,7-dioxa-dibenzo[a,d]cyclooctene (404 mg, 1.0 mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (238 mg, 1.0 mmol) in dry toluene (6 mL) was added potassium carbonate (276 mg, 2.0 mmol) and 18-crown-6 (528 mg, 2.0 mmol). The mixture was heated at 60 °C for 16 h. The mixture was filtered, and concentrated in vacuo. The residue was submitted to flash chromatography using toluene/ethyl acetate (19:1) as eluent to give 297 mg (53%) of the title compound; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 3H), 1.25 (t, 3H), 2.96 (d, 2H), 3.30-3.42 (m, 1H), 3.55-3.65 (m, 1H), 3.90-3.95 (m, 2H), 4.0 (t, 1H), 4.15-4.25 (m, 4H), 4.55 (d, 1H), 5.87 (d, 1H), 6.18 (s, 1H), 6.88-6.95 (m, 4H), 7.10-7.25 (m, 4H), 7.60 (d, 2H).

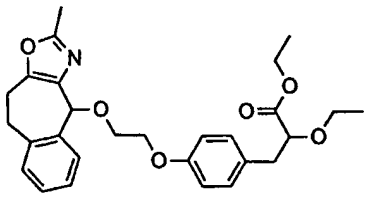
EXAMPLE 6



3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid

3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester (example 5) (450 mg, 0.8 mmol) in ethanol (8 mL) was added NaOH 1N (4.0 mL, 4.0 mmol).The mixture was stirred at room temperature for 16 h. The sodium salt of the title compound was isolated by filtration and washed with ethanol/water to give 272 mg (61%): m.p. 240-241°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (t, 3H), 2.55-2.65 (m, 1H), 2.80-2.88 (m, 1H), 3.05-3.15 (m, 1H), 3.48-3.60 (m, 2H), 3.80-3.90 (m, 2H), 4.15-4.25 (m, 2H), 4.65 (d, 1H), 5.90 (d, 1H), 6.13 (s, 1H), 6.85 (d, 2H), 7.05 (d, 2H), 7.15 (d, 2H), 7.23-7.30 (m, 2H), 7.55-7.58 (m, 2H).

EXAMPLE 7



2-Ethoxy-3-(4-[2-(2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-ethoxy]-phenyl)-propionic acid ethyl ester

a)

To a ice cooled solution of oxazol (1.08 g, 5.0 mmol) in dry THF (50 mL) was added sodium hydride (500 mg of 60 % mineral oil dispersion, 10 mmol). After stirring for 20 min. *tert*-butyl bromoacetate (1.95 g, 10 mmol) was added. Stirring at room temperature for 1 h. The reaction mixture was quenched with water and the product extracted with ethyl acetate (2 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to give 1.47 g (90%) of (2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-acetic acid *tert*-butyl ester.

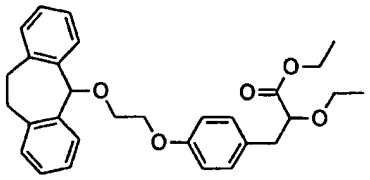
b)

To a solution of (2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-acetic acid *tert*-butyl ester (1.4 g, 4.3 mmol) in dry ether (10 mL) was added a suspension of lithium aluminum hydride (245 mg, 6.5 mmol) in dry ether (40 mL). Stirring at room temperature for 1.5 h. The reaction was quenched with water an the product extracted with ether. The combined ether phases were dried $MgSO_4$, filtered and concentrated in vacuo to give 900 mg (91%) of 2-(2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-ethanol.

c)

Under a nitrogen atmosphere, 2-(2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-ethanol (400 mg, 1.6 mmol), tributylphosphine (480 mg, 2.4 mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (380 mg, 1.6 mmol) were successively dissolved in dry benzene (10 mL). Solid azodicarboxylic dipiperidine (ADDP) (480 mg, 2.4 mmol) was added under stirring at 0 °C to the solution. After 10 min, the reaction mixture was brought to room temperature and the stirring was continued for 16 h. The mixture was added water and the product extracted with ethyl acetate. The combined organic phases was dried ($MgSO_4$), and concentrated in vacuo. The residue was purified chromatography eluting with petroleum ether/ethyl acetate (1:1) to give 300 mg (40%) of the title compound: ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H). 1.20 (t, 3H), 22.38 (s, 3H), 2.60-2.85 (m, 2H), 2.90-3.05 (m, 3H), 3.25-3.38 (m, 1H), 3.52-3.65 (m, 1H), 3.65-3.75 (m, 1H). 3.75-3.90 (m, 2H), 3.95 (t, 1H), 4.05 (t, 2H), 4.15 (q, 2H), 5.25 (s, 1H), 6.75 (d, 2H), 7.10 (d, 2H), 7.13-7.30 (m, 4H).

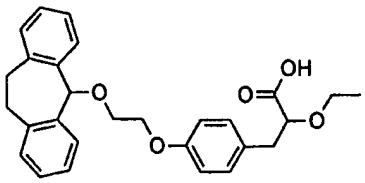
EXAMPLE 8



3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propanoic acid ethyl ester

A mixture of 5-(3-mesyloxypropylidene)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten (5.0 g, 15.2 mmol), ethyl 3-(4-hydroxyphenyl)-2-ethoxypropanoate (3.7 g, 15.5 mmol), potassium carbonate (2.9 g, 21 mmol) and dimethylformamide (10 ml) was heated at 100 °C for 5 h. Benzene (200 ml) and water (200 ml) were added and the phases were separated. The organic phase was dried and the solvent evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with benzene/chloroform, to give first 2.5 g of 5-propenylidene-10,11-dihydro-5H-dibenzo(a,d)cyclohepten and then 1.5 g (21%) of the title compound as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.10-7.35 (m, 10 H); 6.85 (d, 2 H); 6.06 (t, 1 H); 4.27 (q, 2 H); 4.07 (m, 3 H); 3.68 (m, 1 H); 3.45 (m, 1 H); 3.17 (bs, 4 H); 3.06 (d, 2 H); 2.69 (q, 2 H); 1.27 (t, 3 H); 0.99 (t, 3 H).

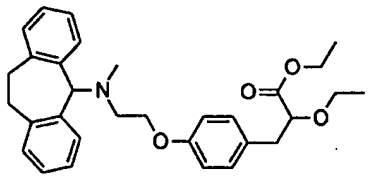
EXAMPLE 9



3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propanoic acid

3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propanoic acid ethyl ester (example 8) (1.5 g, 3.2 mmol) was dissolved in ethanol (30 ml) and 20% sodium hydroxide (3 ml) was added. After 3 days ethanol was evaporated in vacuo, water (50 ml) and hydrochloric acid (2 ml) were added and the mixture was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue (1.1 g, 78 %) was dissolved in ethanol and treated with (L)-lysine monohydrate (0.41 g). Ethanol was evaporated and the residue triturated with diethyl ether. The crystalline product was filtered off and dried in the air. This afforded 1.45 g of the title compound as salt with (L)-lysine (dihydrate). M.p. 148-150 °C. ^{1}H NMR (250 MHz, DMSO-d_6 δ 7.00-7.35 (m, 10 H); 6.75 (bd, J=8.2 Hz, 2 H); 6.26 (bs, 8 H); 5.91 (t, J=6.6 Hz, 1 H); 4.02 (t, J=6.2 Hz, 2 H); 3.76 (m, 1 H); 3.59 (m) + 3.31 (m), 2 H; 3.07 (bs (4 H); 2.70-2,95 (m, 4 H); 2.51 (bq, 2 H); 1.66 (bm, 6 H); 1.03 (t, J=7.2 Hz, 3 H).

EXAMPLE 10

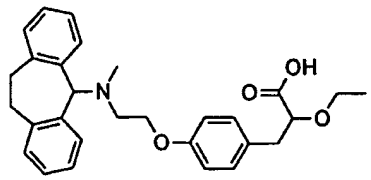


3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid ethyl ester

A mixture of 5-(methylamino)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene hydrochloride(1.8 g, 6.94 mmol), ethyl 3-(4-bromethoxyphenyl)-2-ethoxypropanoate (2.4 g, 6.95 mmol), potassium carbonate (2.9 g, 21 mmol) and dimethylformamide (7 ml) was heated at 100 °C for 5 h. Benzene (200 ml) and water (200 ml) were added and the phases were separated. The organic phase was dried and the solvent evaporated in vacuo. The residue was purified by

chromatography on silica gel eluting with benzene/chloroform to give 2.2 g (65 %) of the title compound as an oil. RF=0.60 (chloroform/ethanol/ammonia=20:2:0.1)

EXAMPLE 11



3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid

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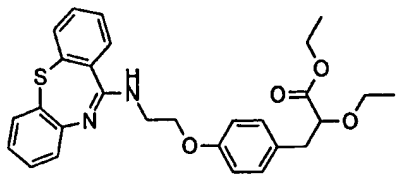
3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid ethyl ester (example 10)(1.5 g, 3.07 mmol) was dissolved in ethanol (20 ml) and 20% sodium hydroxide (2 ml) was added. After 6 days ethanol was evaporated in vacuo, water (50 ml) and acetic acid (2 ml) were added and the mixture was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue (1.4 g) was dissolved in acetone and neutralized with solution of hydrogen chloride in diethyl ether. The solvents were evaporated and the residue was triturated with diethyl ether yielding 1.15 g (74 %) of the title compound as amorphous solid (hemihydrate). ^{1}H NMR (250 MHz, DMSO-d_6) δ 10.50 (bs, 1 H); 7.60 (bs) + 7.10-7.50 (m, 10 H), 6.87 (d, J=7.9 Hz, 2 H), 5.84 (bd, J=7.0 Hz, 1 H), 4.49 (bs, 2 H), 4.00 (t, J=5.6 Hz; + bm, 3 H), 3.30-3,60 (m + m, 4 H), 2.80-3.10 (s + bm, 7 H), 1.07 (t, J=7.2 Hz, 3 H).

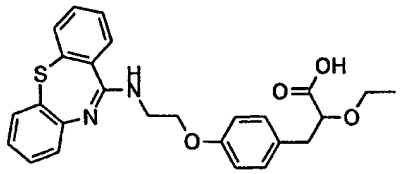
EXAMPLE 12



3-(4-[2-(Dibenzo[b,f]-1,4-thiazepin-11-ylamino)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester

A mixture of ethyl 3-(4-(2-bromethoxy)phenyl)-2-ethoxypropanoate (3.05 g, 8.8 mmol), potassium phtalimide (2.0 g, 10.8 mmol) and dimethylformamide (20 ml) was heated to 100 °C for 16 h, benzene (200 ml) and water (200 ml) were added and the phases were separated. The organic phase was dried and the solvent evaporated in vacuo. The residue was dissolved in ethanol (60 mL), hydrazine hydrate (1.3 ml) was added and the mixture was refluxed for 2 h, filtered and the solvent evaporated to give 2.4 g (96 %) of ethyl 3-(4-(2-aminoethoxy)phenyl)-2-ethoxypropanoate as an oil. Hydrogen oxalate hemihydrate was prepared for characterization by neutralization with oxalic acid in acetone. M.p. 146-148 °C.
A mixture of dibenzo[b,f9-1,4-thiazepin-11(10H)-thione (2.20 g, 9 mmol; prepared as described in Coll.Czech.Chem.Commun. 48, 1465 (1983), 3-(4-(2-aminoethoxy)phenyl)-2-ethoxypropanoic acid ethyl ester (2.60 g, 8.9 mmol) and 3-methyl-1-butanol (70 ml) was stirred and heated at 150 °C for 16 h. The solvent was evaporated in vacuo, dichloromethane (50 ml) and water (50 ml) were added, the mixture was filtered and the phases were separated. The organic phase was dried ($MgSO_4$) and the solvent was evaporated in vacuo to give a residue which was purified by column chromatography on silica gel eluting with chloroform. This afforded 0.7 g of the starting thione and then 1.7 g (38 %) of the title compound as an oil. ^1H NMR (250 MHz, $CDCl_3$) δ 7.05-7.50 (m, 9 H), 6.85-6.95 (m, 3 H), 5.15 (bs, 1 H), 4.25 (m, 2 H), 4.16 (q, J=7.2 Hz, 2 H), 3.96 (t + m, 3 H), 3.59 (m, 1 H), 3.34 (m, 1 H), 2.95 (d, J=6.4 Hz, 2 H), 1.22 (t, J=7.2 Hz, 3 H), 1.16 (t, J=7.2 Hz, 3 H).

EXAMPLE 13



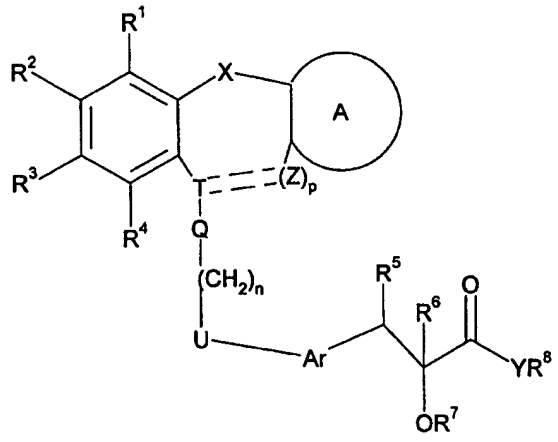
3-(4-[2-(Dibenzo[b,f]-1,4-thiazepin-11-ylamino)-ethoxy]-phenyl)-2-ethoxy-propionic acid

3-(4-[2-(Dibenzo[b,f]-1,4-thiazepin-11-ylamino)-ethoxy]-phenyl)-2-ethoxy-propanoic acid ethyl ester (1.6 g, 3.26 mmol) was dissolved in ethanol (30 ml) and 20% sodium hydroxide (3

ml) was added. After 6 days ethanol was evaporated in vacuo, water (50 ml) and acetic acid (3 ml) were added, the product was filtered off and dried yielding 1.4 g (87 %) of the title compound as hydrate. ^{1}H NMR (250 MHz, DMSO-d6) δ 7.3-7.6 (m, 6 H), 7.10-7.25 (m, 3 H), 6.82-7.15 (m + bs, 4-5 H), 4.26 (bt, J=4.9 Hz, 2 H), 3.88 (dd, J=7.6 Hz and 4.2 Hz, 1 H), 3.78 (bs, 2 H), 3.54 (m) + 3.25 (m), 2 H; 2.91 (bdd, 1 H), 2.70-2.82 (m, 1 H), 1.03 (t, J=7.2 Hz, 3 H).

Claims:

1. A compound of formula (Ia)



(Ia)

wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-12}alkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino, aminoC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, halogen, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

or R^1 and R^2, R^2 and R^3 and/or R^3 and R^4 may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C_{1-6}alkyl;

ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{1-12}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-12}alkyl, amino, acylamino, C_{1-12}alkyl-amino, arylamino, aralkylamino,

aminoC$_{1-12}$alkyl, C$_{1-12}$alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C$_{1-12}$alkoxyC$_{1-12}$alkyl, aryloxyC$_{1-12}$alkyl, aralkoxyC$_{1-12}$alkyl, C$_{1-12}$alkylthio, thioC$_{1-12}$alkyl, C$_{1-12}$alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO$_2$R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, halogen, perhalomethyl, C$_{1-6}$alkoxy or amino optionally substituted with one or more C$_{1-6}$alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(CHR^9)-CH=CH-, -(CHR^9)-CH$_2$-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-, -(NR^9)-S(O$_2$)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)-, -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C$_{1-12}$alkyl, C$_{1-12}$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C$_{1-12}$alkyl-amino, arylamino, aralkylamino, aminoC$_{1-12}$alkyl, C$_{1-12}$alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C$_{1-12}$alkoxyC$_{1-12}$alkyl, aryloxyC$_{1-12}$alkyl, aralkoxyC$_{1-12}$alkyl, C$_{1-12}$alkylthio, thioC$_{1-12}$alkyl, C$_{1-12}$alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{13}, or -SO$_2$R^{14}, wherein R^{13} and R^{14} independently of each other are selected from hydroxy, halogen, C$_{1-6}$alkoxy, amino optionally substituted with one or more C$_{1-6}$alkyl, perhalomethyl or aryl;
T is >N-, >CH-, >C<, -CH$_2$-N<,
Z is -CH$_2$-, =CH-, >N-, -O-, -S-, >CO, >SO, >SO$_2$, >NR^{15}, wherein R^{15} is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C$_{1-12}$alkyl, C$_{1-12}$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C$_{1-12}$alkyl-amino, arylamino, aralkylamino, aminoC$_{1-12}$alkyl, C$_{1-12}$alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C$_{1-12}$alkoxyC$_{1-12}$alkyl, aryloxyC$_{1-12}$alkyl, aralkoxyC$_{1-12}$alkyl, C$_{1-12}$alkylthio, thioC$_{1-12}$alkyl, C$_{1-12}$alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{16}, or -SO$_2$R^{17}, wherein R^{16} and R^{17} independently of each other are selected from hydroxy, halogen, C$_{1-6}$alkoxy, amino optionally substituted with one or more C$_{1-6}$alkyl, perhalomethyl or aryl;
Q is -O-, -S-, >NR^{18}, wherein R^{18} is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C$_{1-12}$alkyl, C$_{1-12}$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C$_{1-12}$alkyl-amino, arylamino, aralkylamino, aminoC$_{1-12}$alkyl, C$_{1-12}$alkoxycarbonyl, aryloxycarbonyl, aralk-

oxycarbonyl, C_{1-12}alkoxyC_{1-12}alkyl, aryloxyC_{1-12}alkyl, aralkoxyC_{1-12}alkyl, C_{1-12}alkylthio, thioC_{1-12}alkyl, C_{1-12}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, $-COR^{19}$, or $-SO_2R^{20}$, wherein R^{19} and R^{20} independently of each other are selected from hydroxy, halogen, C_{1-6}alkoxy, amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl;

U is -O-, -S-, $>SO_2$, $>NR^{21}$, wherein R^{21} is hydrogen or C_{1-6}alkyl,

$T==(Z)_p$ represents a single bond or a double bond,

Ar represents arylene, heteroarylene, or a divalent heterocyclic group optionally substituted with one or more C_{1-6}alkyl or aryl;

R^5 represents hydrogen, hydroxy, halogen, C_{1-12}alkoxy, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R^5 forms a bond together with R^6,

R^6 represents hydrogen, hydroxy, halogen, C_{1-12}alkoxy, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, acyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R^6 forms a bond together with R^5,

R^7 represents hydrogen, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, aryl, aralkyl, C_{1-12}alkoxyC_{1-12}alkyl, C_{1-12}alkoxycarbonyl, aryloxycarbonyl, C_{1-12}alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

R^8 represents hydrogen, C_{1-12}alkyl, C_{4-12}-alkenynyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

Y represents oxygen, sulphur or NR^{10}, where R^{10} represents hydrogen, C_{1-12}alkyl, aryl, hydroxyC_{1-12}alkyl or aralkyl groups or when Y is NR^{10}, R^8 and R^{10} may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C_{1-6}alkyl;

n is an integer ranging from 1 to 4,

p is an integer ranging from 0 to 1,

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxycarbonyl, ary-

loxycarbonyl, aralkoxycarbonyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, $-COR^{11}$, or $-SO_2R^{12}$, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
or R^1 and R^2, R^2 and R^3 and/or R^3 and R^4 may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C_{1-6}alkyl.

3. A compound according to anyone of the preceding claims wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino or aralkoxycarbonylamino.

4. A compound according to anyone of the preceding claims wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, C_{1-7}alkyl-amino, arylamino, aralkylamino, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alky or C_{1-7}alkylthio.

5. A compound according to anyone of the preceding claims wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen, perhalomethyl, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl, aralkyl, hydroxyC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl or aralkoxyC_{1-7}alkyl.

6. A compound according to anyone of the preceding claims wherein R^1, R^2, R^3, and R^4 independently of each other represent hydrogen, halogen or C_{1-7}alkyl.

7. A compound according to anyone of the preceding claims wherein R^1, R^2, R^3, and R^4 represent hydrogen.

8. A compound according to anyone of the preceding claims wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR^{11}, or -SO_2R^{12}, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, perhalomethyl, C_{1-6}alkoxy or amino optionally substituted with one or more C_{1-6}alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy or cyano.

9. A compound according to anyone of the preceding claims wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, acylamino, C_{1-7}alkyl-amino, arylamino, aralkylamino, aminoC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl, C_{1-7}alkylthio, thioC_{1-7}alkyl, C_{1-7}alkoxycarbonylamino, aryloxycarbonylamino or aralkoxycarbonylamino.

10. A compound according to anyone of the preceding claims wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, hydroxyC_{1-7}alkyl, amino, C_{1-7}alkyl-amino, arylamino, aralkylamino, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl, aralkoxyC_{1-7}alkyl or C_{1-7}alkylthio.

11. A compound according to anyone of the preceding claims wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl or C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, C_{1-7}alkoxy, aryl, aralkyl, hydroxyC_{1-7}alkyl, C_{1-7}alkoxyC_{1-7}alkyl, aryloxyC_{1-7}alkyl or aralkoxyC_{1-7}alkyl.

12. A compound according to anyone of the preceding claims wherein ring A represents a 6 membered cyclic ring, optionally substituted with one or more chlorine or methyl groups.

13. A compound according to anyone of the preceding claims wherein ring A represent a phenyl ring.

14. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(CHR^9)-CH=CH-, -(CHR^9)-CH$_2$-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-S(O$_2$)-, -(NR^9)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)- or -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen, halogen, hydroxy, C$_{1-7}$alkyl, C$_{1-7}$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, hydroxyalkyl, amino, acylamino, C$_{1-7}$alkyl-amino, arylamino, aralkylamino, aminoC$_{1-7}$alkyl, C$_{1-7}$alkoxyC$_{1-12}$alkyl, aryloxyC$_{1-7}$alkyl, aralkoxyC$_{1-7}$alkyl, C$_{1-12}$alkylthio, thioC$_{1-7}$alkyl, C$_{1-7}$alkoxycarbonylamino, aryloxycarbonylamino or aralkoxycarbonylamino.

15. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(CHR^9)-CH=CH-, -(CHR^9)-CH$_2$-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-S(O$_2$)-, -(NR^9)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)- or -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen, halogen, hydroxy, C$_{1-7}$alkyl, aryl, aralkyl, C$_{1-7}$alkoxyC$_{1-12}$alkyl, aryloxyC$_{1-7}$alkyl or aralkoxyC$_{1-7}$alkyl.

16. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -(CHR^9)-CH=CH-, -(CHR^9)-CH$_2$-CH$_2$-, -(C=O)-, -O-CH$_2$-O-, -(NR^9)-S(O$_2$)-, -(NR^9)-, -CH=(CR^9)-, -(CO)-(CHR^9)-, -CH$_2$-(SO)-, -S-, -(SO)-, -(SO$_2$)-, -CH$_2$-(SO$_2$)- or -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen.

17. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -O-CH$_2$-O-, -(NR^9)-, -S-, -(SO)- or -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen.

18. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -(NR^9)-CH$_2$-, -O-CH$_2$-O-, -(NR^9)-, -S- or -CH$_2$-O-CH$_2$-, wherein R^9 is hydrogen.

19. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR^9)-, -(CHR^9)-CH$_2$-, -CH=CH-, -O-, -O-(CHR^9)-, -S-(CHR^9)-, -O-CH$_2$-O- or -S-, wherein R^9 is hydrogen.

20. A compound according to anyone of the preceding claims wherein X is -S-.

21. A compound according to anyone of the preceding claims wherein T is >C<.

22. A compound according to anyone of the preceding claims wherein Z is -CH$_2$-, =CH-, >N-, -O-, -S-, >CO, >SO, >SO$_2$.

23. A compound according to anyone of the preceding claims wherein Z is >N-.

24. A compound according to anyone of the preceding claims wherein Q is -O-, -S-, >NR^{18}, wherein R^{18} is hydrogen or C$_{1-7}$alkyl.

25. A compound according to anyone of the preceding claims wherein Q is >NR^{18}, wherein R^{18} is hydrogen.

26. A compound according to anyone of the preceding claims wherein U is -O-.

27. A compound according to anyone of the preceding claims wherein T==(Z)$_p$ represents a double bond.

28. A compound according to anyone of the preceding claims wherein Ar represents arylene optionally substituted with one or more C$_{1-6}$alkyl or aryl.

29. A compound according to anyone of the preceding claims wherein Ar represents phenyl.

30. A compound according to anyone of the preceding claims wherein R^5 represents hydrogen, hydroxy, halogen, C_{1-7}alkoxy, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl or aralkyl, or R^5 forms a bond together with R^6.

31. A compound according to anyone of the preceding claims wherein R^5 represents hydrogen or R^5 forms a bond together with R^6.

32. A compound according to anyone of the preceding claims wherein R^5 represents hydrogen, hydroxy, halogen, C_{1-7}alkoxy, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl or aralkyl, or R^5 forms a bond together with R^6.

33. A compound according to anyone of the preceding claims wherein R^5 represents hydrogen or R^5 forms a bond together with R^6.

34. A compound according to anyone of the preceding claims wherein R^7 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl, aralkyl, C_{1-7}alkoxyC_{1-7}alkyl, C_{1-7}alkoxycarbonyl, aryloxycarbonyl, C_{1-7}alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups.

35. A compound according to anyone of the preceding claims wherein R^7 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl or C_{2-7}-alkynyl.

36. A compound according to anyone of the preceding claims wherein R^7 represents C_{1-2}alkyl.

37. A compound according to anyone of the preceding claims wherein R^8 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

38. A compound according to anyone of the preceding claims wherein R^8 represents hydrogen, C_{1-7}alkyl, C_{4-7}-alkenynyl, C_{2-7}-alkenyl, C_{2-7}-alkynyl, aryl or aralkyl.

39. A compound according to anyone of the preceding claims wherein R^8 represents hydrogen or C_{1-2}alkyl.

40. A compound according to anyone of the preceding claims wherein Y represents oxygen, sulphur or NR^{10}, where R^{10} represents hydrogen, C_{1-7}alkyl, aryl, hydroxyC_{1-7}alkyl or aralkyl groups.

41. A compound according to anyone of the preceding claims wherein Y represents oxygen.

42. A compound according to anyone of the preceding claims wherein n is an integer ranging from 2 to 3.

43. A compound according to anyone of the preceding claims wherein p is 1.

44. A compound according to anyone of the preceding claims wherein A is benzo.

45. A compound according to anyone of the preceding claims wherein X is -O-.

46. A compound according to anyone of the preceding claims wherein X is -S-.

47. A compound according to anyone of the preceding claims wherein Z is -S- and p is 1.

48. A compound according to anyone of the preceding claims wherein Z is $-CH_2-$ and p is 1.

49. A compound according to anyone of the preceding claims wherein X is =CH- and p is 1.

50. A compound according to anyone of the preceding claims wherein $T==(Z)_p$ represents a single bond or a double bond.

51. A compound according to anyone of the preceding claims wherein T is >CH-.

52. A compound according to anyone of the preceding claims wherein T is >C<.

53. A compound according to anyone of the preceding claims wherein Q is -O-.

54. A compound according to anyone of the preceding claims wherein Q is -S-.

55. A compound according to anyone of the preceding claims wherein Q is $>NR^{18}$, wherein R^{18} is H.

56. A compound according to anyone of the preceding claims wherein n is 2.

57. A compound according to anyone of the preceding claims wherein U is -O-.

58. A compound according to anyone of the preceding claims wherein Ar is phenylene.

59. A compound according to anyone of the preceding claims wherein R^5 is H.

60. A compound according to anyone of the preceding claims wherein R^6 is H.

61. A compound according to anyone of the preceding claims wherein R^7 is ethyl.

62. A compound according to anyone of the preceding claims wherein R^8 is H.

63. A compound according to anyone of the preceding claims wherein p is 0.

64. A compound according to anyone of the preceding claims A is a five membered ring containing S.

65. A compound according to anyone of the preceding claims wherein X is $-(CHR^9)-CH_2-$, wherein R^9 is H.

66. A compound according to anyone of the preceding claims wherein X is $-O-(CHR^9)-$, wherein R^9 is H.

67. A compound according to anyone of the preceding claims wherein X is $-S-(CHR^9)-$, wherein R^9 is H.

68. A compound according to anyone of the preceding claims wherein X is $-O-CH_2-O-$.

69. The compound according to claim 1 which is:
2-Ethoxy-3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yloxy)-ethoxy]-phenyl}-propionic acid,
3-(4-[2-(Dibenzo[b,f]-1,4-thiazepin-11-ylamino)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,
3-{4-[2-(Dibenzo[*b,f*][1,4]thiazepin-11-ylamino)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
3-{4-[2-(10,11-Dihydro-dibenzo[*b,f*]thiepin-10-ylsulfanyl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,
3-(4-[2-[5*H*-Dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,
3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,
3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid,
3-(4-[2-(6,11-Dihydrodibenzo[b,e]oxepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,
3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,
3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid,
2-Ethoxy-3-(4-[2-(2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-ethoxy]-phenyl)-propionic acid ethyl ester,
3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propanoic acid ethyl ester,
3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propanoic acid,
3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid ethyl ester,
3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid;
or a pharmaceutically acceptable salt thereof.

70. The compound according to claim 1 which is:
2-Ethoxy-3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yloxy)-ethoxy]-phenyl}-propionic acid,

3-{4-[2-(Dibenzo[*b,f*][1,4]thiazepin-11-ylamino)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(10,11-Dihydro-dibenzo[*b,f*]thiepin-10-ylsulfanyl)-ethoxy]-phenyl}-2-ethoxy-propionic acid;

or a pharmaceutically acceptable salt thereof.

71. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

72. A composition according to claim 71 in unit dosage form, comprising from about 0.05 to about 100 mg, preferably from about 0.1 to about 50 mg of the compound according to any-one of the preceding compound claims or a pharmaceutically acceptable salt thereof.

73. A pharmaceutical composition useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the composition comprising, as an active ingredient, a compound according to any-one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

74. A pharmaceutical composition useful in the treatment and/or prevention of diabetes and/or obesity, the composition comprising, as an active ingredient, a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

75. A pharmaceutical composition for diabetes and/or obesity, the composition comprising, as an active ingredient, a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

76. A pharmaceutical composition according to any one of the claims 71-75 for oral, nasal, transdermal, pulmonal, or parenteral administration.

77. A method for the treatment of ailments, the method comprising administering to a subject in need thereof an effective amount of a compound according to anyone of the preceding

compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding composition claims.

78. A method for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to anyone of the preceding claims 71-76.

79. A method for the treatment and/or prevention of diabetes and/or obesity, the method comprising administering to a subject in need thereof an effective amount of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to anyone of the preceding claims 71-76.

80. The method according to claims 77-79, wherein the effective amount of the compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt or ester thereof is in the range of from about 0.05 to about 100 mg per day, preferably from about 0.1 to about 50 mg per day.

81. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament.

82. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

83. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of diabetes and/or obesity.

84. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of diabetes and obesity.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00572

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 69/734, C07C 59/72, C07D 313/12, C07D 321/12, C07D 337/12, C07D 281/16, C07D 263/52, A61K 31/185 31/215,31/335,31/357,31/38,A61K 31/554,31/423, A61P 3/04, 3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9919313 A1 (DR. REDDY'S RESEARCH FOUNDATION), 22 April 1999 (22.04.99) --	1-84
X	STN International, File CAPLUS. CAPLUS accession no. 1998:430714, Document no. 108904, Fukazawa, Nobuyuki et al: "Preparation of hydroxybenzoic acids, their use as cell adhesion inhibitors, and their pharmaceutical compositions", JP,A2,10182550, 19980707 --	1-84
X	WO 9604260 A1 (SMITHKLINE BEECHAM PLC), 15 February 1996 (15.02.96) --	1-84

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" erlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2000	22 -02- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/Els Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00572

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9604261 A1 (SMITHKLINE BEECHAM PLC), 15 February 1996 (15.02.96) --	1-84
X	WO 9725042 A1 (SMITHKLINE BEECHAM P.L.C.), 17 July 1997 (17.07.97) --	1-84
A	WO 9736579 A1 (GLAXO GROUP LIMITED), 9 October 1997 (09.10.97) --	1-84

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00572

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 77-80
because they relate to subject matter not required to be searched by this Authority, namely:

see next page

2. ☒ Claims Nos.: 1-84
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The definition of ring A as a 5-6 membered cyclic ring and Ar as arylene, heteroarylene or a heterocyclic group is too broadly formulated to permit an adequate search. The search has essentially been limited to compounds that are supported by the examples.

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00572

Claims 77-80 relate to methods of treatment of the human or animal body by surgery or by therapy./diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/DK 99/00572

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9919313 A1	22/04/99	NONE	
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		GB 9509923 D	00/00/00

INTERNATIONAL SEARCH REPORT

information on patent family members

02/12/99

International application No.
PCT/DK 99/00572

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		CN 1212622 A	31/03/99
		CZ 9802163 A	17/02/99
		EP 0815091 A	07/01/98
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		NO 983147 A	08/09/98
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WO 9736579 A1	09/10/97	AU 2506197 A	22/10/97
		GB 9606805 D	00/00/00